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UNDERGRADUATE MEDICAL RESEARCH AT THE UNIVERSITY OF TORONTO

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University of Toronto

Medical Journal

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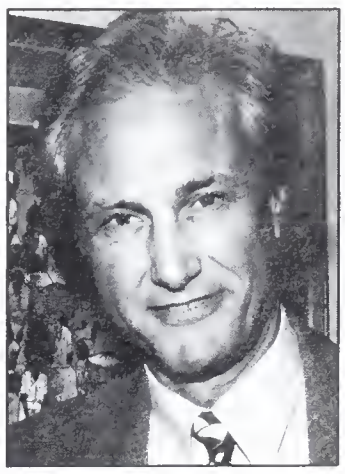
MESSAGE FROM THE VICE-DEAN, EDUCATION



Dr. Andrew Baines

Welcome to the Faculty of Medicine's ninth annual Medical Student Research Day. Each year, this event provides an opportunity for our undergraduate students to display the wide spectrum of research projects they have completed, often during summer fellowships. These projects range from investigations of basic cellular activity to studies of clinical applications in hospitals and community involvement, highlighting the many career paths open to Faculty of Medicine students.

Taking a research project from concept to completion provides a stimulating learning experience, giving undergraduates the opportunity to discover if they have the self-discipline, dedication and creative thinking required to be a successful investigator. As Vice-Dean of Education, I am proud to say that many of our undergraduates do have these qualities. Our Faculty has a great tradition of research breakthroughs, and it is my hope than many of the students involved in today's Medical Student Research Day will continue that tradition. Congratulations to all the participants - and many thanks to the faculty members who made this year's event possible.

Andrew Baines, MD, PhD

MEDICAL RESEARCH - THE CHALLENGE FOR PHYSICIANS

Dr. Catharine Whiteside

Dr. Michael Pare

Numerous medical students at the University of Toronto are engaged in research. Each summer approximately 100 medical students receive scholarships through the Faculty of Medicine enabling them to work on projects in basic science laboratories and clinical investigative settings. Approximately 40% of the students who apply are funded based on scholarship and merit of the research proposed. They, and the students in the MD-PhD research programme, present their work at Medical Student Research Day to colleagues and faculty members. The top-rated students in the categories of basic and clinical research, receive an all-expense paid trip to the Annual Medical Student Research Forum (U.S.A.) in Galveston, Texas, in April, representing our Faculty. The Department of Medicine also supports the top-rated student (in either category), supervised by one of its members, to attend the same meeting.

The undergraduate students in the Division of Biomedical Communications, Department of Surgery, also present their original and creative work in poster format at Research Day.

Why do students wish to extend their professional training into the realm of biomedical research? There are many reasons including scientific curiosity, extension of previous engagement in research (an increasing number of medical students hold graduate degrees), desire to work with specific faculty members in clinical or research specialties. Many of the students will contribute to scientific papers published in peer-reviewed journals. Some will seek future career development as Clinician-Scientists, entering graduate or post-graduate research programmes during or after clinical specialty training. The Faculty of Medicine at the University of Toronto is a major focus of basic and clinical investigation in Canada and in many fields has developed an international reputation for excellence in research. It is no wonder that our medical students wish to share in this expertise and take advantage of the rich learning environment.

At Research Day 1994-95, Professor Lap-Chee Tsui from the Department of Medical and Molecular Genetics,

Hospital for Sick Children Research Institute, addressed the students and faculty discussing, "Cystic fibrosis: understanding the disease from the gene". Professor Tsui is the co-discoverer of the CFTR gene and with his team and colleagues continues to explore its mechanism of action and molecular regulation. He is a legend in his own time and a truly inspirational figure in our medical research community.

The students participating in research day have taken time out of a demanding professional training programme to prepare and present their posters. The challenge for health care professionals engaged in research is to maintain a balance between clinical and investigative responsibilities. The students who participate in Research Day begin to experience this sometimes difficult, yet highly rewarding, duality. Their remarkable enthusiasm displayed at Research Day indicate this challenge as both exciting and enjoyable. Clinician-Scientists, who desire to bridge the conceptual and practical gap from bench-to-bedside, are uniquely suited for their role as career investigators, teachers and physicians.

Diana Alli

The students and Faculty are indebted to Ms. Diana Alli, Coordinator, Office of Student Affairs, and the Medical Student Committee who worked so hard and efficiently in the planning and preparation for Research Day. Thanks to the students, their supervisors and the judges who participated in this academic highlight. The Research Day Co-ordinators, on behalf of the Faculty, wish to express their gratitude to the corporate sponsors for their generous support.

Catharine Whiteside, MD, PhD
Michael Pare, MD, MSc
Co-ordinators of Medical Student Research Day

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1. WORKSTATION DESIGN AND WORK HABITS: THEIR ASSOCIATION WITH MUSCULOSKELETAL PAIN IN VIDEO DISPLAY TERMINAL USERS.

Daphne L. Anderson, BSc., MPE and Nancy McKee, BSc., MD, FRCS(c), FACS. Professor of Surgery, Mount Sinai Hospital, University of Toronto

The purpose of this study was to identify workstation characteristics (extrinsic factors) and employee work habits (intrinsic factors) associated with reported musculoskeletal (MSK) pain symptoms. In order to measure MSK pain symptoms a questionnaire was developed and administered both before and after an intervention. The intervention consisted of a workstation environment change from "non ergonomic/ non-adjustable" workstations to "ergonomic/ adjustable" Technion workstations. An additional intervention was attempted with 9 employees which involved an educational seminar which included implementation of the Canadian Center for Occupational Health and Safety (CCOHS) standard recommendations for video display terminal (VDT) workstations and recommended user mechanics.

The study population consisted of 66 CTV television employees. These results refer to the data collected prior to the intervention only, further data results will soon follow. Greater than 50% of all employees claimed to have worked with computers for longer than 5 years. 42% used the keyboard an average 4 hours or longer every work day. 79% requested at least one change to their workstation. 42% of employees requested changes to their chairs where 34% of those were requests for increased back support. 22 requests were made for an adjustable keyboard tray. 82% of employees reported that they did not consider their workstations to be adjustable and furthermore 65% of those did not feel they had the knowledge to properly adjust a workstation regardless of its availability.

Reports of MSK pain included the following where 42%, 31%, 46%, 45%, and 49% had hand, wrist, shoulder, neck, and lower back pain respectively. The majority of employees described their pain as moderate to severe.

Statistical analysis using SAS and Chi squared analysis showed no significant relationship between MSK pain and age or sex or level of fitness. Employees who experienced MSK pain were more likely to seek medical attention and those who experienced back pain were more likely to request changes in their chair ($p<0.05$).

No relationship was established between reports of MSK pain and those individuals who worked longer hours (>8/day and > 40/week) or those who took fewer breaks or those who requested more workstation changes. The preliminary results of this study showed that there was a large proportion of employees who requested a change to their workstation. There was a surprisingly large percentage who reported MSK pain. Finally, this study reported that there may be a need to further educate employees with regards to favorable work habits and optimal workstation/user ergonomics.

2. THE 3T3-L1 CELL LINE AS A MODEL FOR STUDYING THE EFFECT OF ACYLATION-STIMULATING PROTEIN ON HUMAN ADIPOCYTE DIFFERENTIATION

Alexis Armour, B.Sc., Magdalena Maslowska, B. Sc., Katherine Cianflone, B. Sc., Ph. D., Allan D. Sniderman, M.D., F.R.C.P., McGill Unit for the Prevention of Cardiovascular Disease, Royal Victoria Hospital, Montreal, Que.

Although it is has been established that obesity and certain hyperlipidemias are risk factors for atherosclerosis, many questions remain concerning the lipid pathophysiology of these disorders. Acylation-Stimulating Protein (ASP), a human plasma protein which markedly stimulates triglyceride synthesis in cultured human skin fibroblasts and human adipocytes, is currently being investigated for its role in lipid metabolism. Preliminary results on the effect of ASP on the differentiation of human adipocytes have been encouraging. However human adipocyte differentiation in culture presents certain practical problems. The aim of this study is to assess the viability of the 3T3-L1 cell line as a model for the study of ASP's effects on adipocyte differentiation.

Several potential 3T3-L1 differentiation protocols were developed in an attempt to demonstrate the effects of ASP. The relative extents of differentiation of the cells under the different culture conditions were then assessed. It could not be clearly shown, under any of the experimental conditions used in this study, that ASP affected 3T3-L1 adipocyte differentiation.

This preliminary study indicates that much more work is necessary to develop a viable approach to the study of ASP's effects on differentiation, using 3T3-L1 preadipocytes. It can be concluded that, under our experimental conditions, 3T3-L1 preadipocyte culture could not be used to study ASP's effects on adipocyte differentiation; it appears therefore that human adipocytes are better suited for research in this area of lipid physiology.

3. STATIC AND DYNAMIC STRESS ANALYSIS AT GRAFT-ARTERY JUNCTIONS

Peter D. Ballyk[1,2], Colin Walsh[2,3] and Shu-Yu Zhu[3]
Faculty of Medicine[1], Institute of Biomedical Engineering[2], and Department of Electrical and Computer Engineering[3], University of Toronto, Canada

Cardiovascular disease is the leading cause of death in the western world, and atherosclerosis accounts for the majority of these deaths. Treatment for advanced atherosclerotic lesions usually involves surgical bypass graft implantation. Unfortunately, many grafts become occluded one or more years after implantation due to intimal hyperplasia at the distal graft-artery anastomosis.

Many studies have shown that bypass grafts are more likely to remain patent if the graft and artery material properties are matched. Also, it has recently been shown that cyclic stretch of cultured endothelial monolayers leads to the production of growth factors promoting intimal hyperplasia. This evidence suggests that the vascular wall mechanics at graft-artery junctions may play an important role in graft failure. Our hypothesis is that the mismatch between graft and artery material properties results in abnormal mechanical stresses at the graft-artery junction, and promotes intimal hyperplasia.

In the present study, the mechanics of an end-to-end graft-artery junction (like that used in aortic aneurysm repairs) were modeled using computer simulation techniques. Various graft materials (vein, Dacron, and PTFE) were simulated under both static and dynamic conditions. Large differences between graft and artery material properties resulted in large spatial gradients in stress local to the graft-artery junction. Large stress gradients did not occur when the material properties were matched, suggesting that the gradient of stress at the junction may contribute to intimal hyperplasia.

Further studies are currently underway to determine the effect that intimal hyperplasia has on stress gradients at graft-artery junctions.

4. SHOULDER INSTABILITY: CURRENT CONCEPTS

P. Joy Banerjee, Paul H. Marks, BA Sc, MD, FRSCS, Surgical Staff, Orthopaedic and Arthritic Hospital

Glenohumeral instability is a very common finding, especially in athletes. Accurate diagnosis relies on a thorough history and physical examination. One needs to ascertain the nature of onset, direction of instability and type of activities which aggravate the shoulder. On physical examination, the apprehension test is quite useful in cases of anterior instability, but is less so in posterior instability. Radiologic investigations include radiographs, computed tomography, arthrotomography and magnetic resonance imaging. Diagnostic accuracy, cost and waiting time are all issues that must be addressed when considering their use. Nonoperative treatment includes closed reduction followed by immobilization and an exercise regimen. No consensus has been reached with respect to the efficacy of the nonoperative treatment. However, there is a known documented high recurrence rate in the younger atraumatic anterior instability population. Operative treatment includes arthroscopic and open repair. Some of the more traditional open repair procedures have fallen out of favour as a result of long term complications. Procedures which have addressed capsular laxity and excessive joint volume have yielded higher success rates. However, regardless of the procedure chosen, it has been a common finding that the throwing athlete has difficulty returning to his/her previous level of performance. Rehabilitative programs are aimed at returning full range of motion, strength and functional retraining.

5. EXPRESSION OF MARKERS OF NEUTROPHIL ACTIVATION FOLLOWING ABDOMINAL AORTIC ANEURYSM REPAIR

Greg Belchetz, Jairie Ferasol, Thomas F. Lindsay, M.D., F.R.C.S.C., Division of Vascular Surgery, The Toronto General Hospital

Ruptured abdominal aortic aneurysms are responsible for a significant number of deaths in individuals over 55 years of age. The mortality rate for those who arrive at the hospital with a ruptured AAA is 50% to 70%, whereas the mortality rate for those undergoing elective AAA repair is 3% to 5%. It is thought that the combination of hypotension (due to the ruptured AAA) and lower torso ischemia/reperfusion (required for AAA repair) may result in neutrophil activation which may then mediate remote organ injury and contribute to the high mortality rate. This study seeks to determine changes in expression of neutrophil activation markers during AAA repair and whether there is a difference in neutrophil activation between ruptured and elective AAA patients. L-selectin and Mac-1 surface antigens were markers used to measure neutrophil activation. CD 63 and CD 67 were used to measure neutrophil degranulation during activation.

Nine patients undergoing elective AAA repair and two patients with ruptured AAA were studied. Blood samples were obtained at regular time intervals during and after surgery. Neutrophil markers were labeled with monoclonal antibodies bearing fluorescent tags and surface expression was quantified using flow cytometry. L-selectin expression increased steadily and peaked at 1 hour post clamp removal (PCR), then declined to initial values by 24 hours PCR. Mac-1 expression increased at 24 hours PCR and began to decline at 72 hours PCR. L-selectin and Mac-1 expression were consistently greater in patients with ruptured aneurysms compared with elective patients.

Preliminary results show striking upregulation of neutrophil degranulation markers in elective AAA patients. This study shows that markers of neutrophil activation are upregulated during elective AAA repair and expression is markedly higher in ruptured AAA patients.

6. THE ISOLATION AND PARTIAL CHARACTERIZATION OF FOUR NEW MYELIN BASIC PROTEINS

Chris Boulias, PhD, Henrianna Pang, PhD* and Mario Moscarello, MD, PhD Biochem Research, Hosp. for Sick Children and *Carbohydrate Research Center, MSB

Myelin is a specialized multilammelar membrane system which facilitates saltatory conduction of impulses along axons of the nervous system. The myelin basic proteins (MBPs) which are extrinsic membrane proteins accounting for 35% of the total protein in CNS myelin, are important in its organization and maintenance. The MBPs have been linked to multiple sclerosis (MS) because they induce allergic encephalomyelitis (considered to be a model of MS) in laboratory animals.

The unbound fraction from CM52 columns, used to isolate the various components of MBP, was used as the source of at least four additional MBP molecules. We routinely obtain two major fractions called C8-A and C8-B from CM52 columns on which an acidic extract of human white matter has been applied. The C8-A and C8-B fractions were further purified on HPLC. Each contained two proteins in the 17-18 kDa range which we called C8-A(H) (higher Mr) and C8-A(L) (lower Mr). In order to obtain amino acid compositions, each band was transferred electrophoretically to immobilon membranes for amino acid analyses. The citrulline values were high in three of the four proteins, which was accompanied by a compensatory decrease in the arginine values. All other residues were present in similar amounts. These compositions clearly identify these four proteins with the citrullinated form of MBP. Western blot analysis showed that both H and L forms reacted with an anti MBP antibody. Sequence analysis of the two proteins in the C8-B fraction identified these proteins as MBP. Mass spectrometry of the C8-B(H) and C8-B(L) provided us with an accurate mass of 18, 558.08 ± 8.13 and 17,266.63 ± 2.24 respectively. We concluded that the H and L proteins were MBP's.

The origins of these proteins is not known at this time. With the isolation of the larger MBP gene (Golli-mbp) and reports of embryonic forms of MBP (Mr≈16 kDa), it is likely that the proteins in the C8 fraction are not degradative products but are translated from specific mRNA's. Their functional significance is obscure. The possibility that they are found in early forms of myelin or as components of transitional membranes between oligodendrocytes and myelin cannot be discounted.

7. THE EVOLUTIONARY CHANGES OF THE UNIVERSITY OF TORONTO MEDICAL SCHOOL UNDERGRADUATE CURRICULUM

Joan Saary, MSc & Chris Boulias, PhD

Since its inauguration in 1843, the Faculty of Medicine at the University of Toronto has seen many changes in its undergraduate medical curriculum. In this paper we will present the ideological changes that have occurred over the years, as well as how these changes have been instituted in medical education.

Over time a curriculum is affected by influences and pressures from external factors. Examples of such factors have included rapid advances in areas such as computer and laboratory technology, as well as in the basic sciences. It is well recognized that medicine is both an art and a science. Changes such as those described above have in the past tipped the scale towards the science and away from the art. As a result, within this context the focus of student learning had been the book rather than the patient. The most recent change in the curriculum at the University of Toronto has been a shift from a didactic perspective to a curriculum based on the following guidelines: 1. patient centered learning, 2. integrated and multidisciplinary content, 3. student motivated learning, and 4. structured problem based learning.

Curriculum changes are a reflection of the dynamic nature of medicine, how it is taught and practiced. Over 100 years of curriculum development will be presented from a historical perspective.

8. ADOLESCENT SEXUAL OFFENDERS IN RESIDENTIAL TREATMENT AND ON FOLLOW-UP

Jennifer Burgess, Helen O'Halpin, M.D., Staff Psych. C.M. Hincks Treatment Centre - Div. Child Psychiatry, U of T

The characteristics of 13 adolescent sexual offenders disclosed from a Residential Treatment program, and their families, were explored, through chart review and follow-up by phone/mail. This study seeks to examine the links between childhood and intergenerational sexual abuse, multiple disruptions of attachments and later sexual offender behaviour. Efficacy of treatment continues to be evaluated by ongoing collection of data re offences after discharge.

The early results indicate severe family psychopathology and multigenerational patterns of abuse; thus far, a remarkably low occurrence of charges for sexual offences post-discharge may indicate a positive response to treatment.

9. RELATIONSHIP BETWEEN IL-1 AND IL-6 IN THE PATHOGENESIS OF FEVER

Rodrigo B. Cavalcanti, E.S. Akarsu, Flavio Coceani, Div. of Neurosciences, Research Institute, Hospital for Sick Children, Dept. of Physiology - U of T

One of the current hypotheses in fever research is that IL-1 acting in the brain is important in stimulating the anterior hypothalamus to regulate body temperature so as to reach higher values. However, IL-6 injected intracerebroventricularly (icv) has also been shown to cause fever, suggesting that IL-1 is not the only cytokine mediating fever centrally. Based on these observations, two possible schemes for the action of these cytokines were hypothesized: a) Following endotoxin challenge IL-1 is synthesized in the brain, triggering in turn the synthesis of IL-6 or b) endotoxin injection causes the simultaneous synthesis of both IL-1 and IL-6 in the brain. An answer to this question is made possible by the availability of a specific IL-1 receptor antagonist (IL-1ra). The purpose of this project was to distinguish between the two schemes by measuring IL-6 levels in the cerebrospinal fluid (CSF) in the course of fever. Conscious cats fitted with colonic and ear thermistor probes were given icv injections of either endotoxin or human recombinant IL-1ß. Treatments were performed alone and with a prior treatment of 3 x Iµg IL-1ra icv. Intravenous endotoxin injections were also performed in order to evaluate responses to peripheral pyrogen challenges. CSF samples were taken before pyrogen injection and during latent period, fever uprise and fever plateau phases. IL-6 levels in the CSF were determined by bioassay using the 7TD hybridoma cell line. Fever responses were evaluated by calculating fever latency, peak time and magnitude, and thermal response index. Results show induction of IL-6 in the CSF following icv endotoxin injections, which is not affected by IL-1ra treatment. This supports the simultaneous synthesis of IL-1 and IL-6 following icv endotoxin injections, thereby pointing towards a synergistic effect of these cytokines in brain during the febrile response.

[RBC was supported by a summer scholarship from U of T Fac. of Medicine]

10. VARUS TALAR NECK MALALIGNMENT: A RADIOGRAPHIC ANALYSIS

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Although fractures of the neck of the talus are relatively uncommon, their significance arises from a high associated morbidity and difficulty in the adequate assessment of the quality of reduction. The objective of this study was to develop a clinically applicable method of evaluating talar neck malalignment in the transverse plane. In the standard anteroposterior radiographic projection, surrounding osseous structures make direct radiographic visualization of the talar neck in the transverse plane difficult. Therefore, in this study, forefoot position relative to hindfoot position was assessed to determine if it reflects varus malalignment of the talar neck. In addition, the angle between the longitudinal axes of the talar head and body was measured to determine if it reflects the malalignment.

Thirteen above/below-knee amputations were radiographed before and after the creation of a varus malalignment at the talar neck, via a medially-based, closing wedge osteotomy. The amount of varus talar neck malalignment created was obtained from the direct measurement of the angular displacement between two initially parallel K-wires placed into the talar body and head. The radiographs before and after the talar neck malalignment were analyzed and compared to the results obtained from direct measurement.

The average amount of varus created at the talar neck was 17.5°± 4.3°. Angles based on forefoot-hindfoot relationships did not reveal any statistically significant changes following varus malalignment. The angle between the longitudinal axes of the talar head and body significantly changed from 19°± 7° to 28°± 8° ($P<0.005$).

This study showed that radiographic analysis of foot position based on internal foot relationships (i.e., forefoot vs. hindfoot positions) did not significantly reflect varus talar neck malalignment. However, the angle between the longitudinal axes of the talar head and body did significantly reflect the malalignment and may represent a clinically applicable method of evaluating talar neck malalignment in the transverse plane.

11. THE ROLE OF ANTI-RO AND ANTI-LA ANTIBODIES IN PREDICTING CLINICAL MANIFESTATIONS OF NEONATAL LUPUS ERYTHEMATOSUS

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Neonatal lupus erythematosus (NLE) is a disease of the newborn resulting from the transplacental transfer of maternal anti-Ro and anti-La autoantibodies, causing manifestations such as dermatitis and congenital heart block (CHB). Most women positive for these antibodies, however, deliver normal children. This study aims to examine the value of measuring anti-Ro and anti-La antibody levels in predicting outcome in NLE.

Sera collected from 154 women positive for anti-Ro and anti-La antibodies during pregnancy were included in this study: 94 had normal children, 24 had children with CHB and 36 had children with dermatitis. Antibody levels were measured using the ELISA technique and expressed in units of OD. The limit of normal was <300 units, determined by testing sera from 100 pregnant women negative for anti-Ro and anti-La antibodies.

Results:

mean values (units OD)

Diagnosis	anti-Ro	anti-La
normal	5500±1338	1290±293
CHB	18485±4960*	9821±4362*
dermatitis	14202±3104*	17340±4375*

** $p<0.001$ as compared to normal. There were no statistically significant differences between CHB and dermatitis for both anti-Ro and anti-La antibodies.*

Regression analysis revealed that there was a statistically significant correlation between anti-Ro and anti-La antibody levels in women who had children with dermatitis ($R=0.416$; $p=0.01$) but not for women who had children with CHB ($R=0.122$; $p=0.57$).

Conclusions: Statistically significant differences in anti-Ro and anti-La antibody levels were seen between women who had normal children and women who had children with CHB or dermatitis. There was appreciable overlap, however, as not all women with high antibody levels delivered children with NLE. Anti-La antibody levels were higher for dermatitis than for CHB, while anti-Ro antibody levels were almost equivalent for the two diagnoses, indicating differences in the autoantibody profile versus the La protein in particular. Although quantitative differences were observed for anti-Ro and anti-La antibodies in CHB and dermatitis, these autoantibody profiles do not have predictive value in determining outcome in NLE.

12. REFLEX EFFECT OF FOREARM VENOUS OCCLUSION ON PERONEAL MUSCLE SYMPATHETIC NERVE ACTIVITY

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Objective: Congestive heart failure is characterized by sympathetic excitation. The relative contribution of venous congestion to this sympathetic activation is not known. Our objective was to determine whether forearm venous occlusion in normal subjects elicits a reflex increase in muscle sympathetic activity.

Design and Methods: We studied seven healthy male subjects, aged 21±1.4 yrs (mean±s.d.) on two separate days. Subjects lay supine in a quiet, awake, eye-open state. A standard adult size blood pressure cuff was wrapped around the right arm. The cuff was inflated sequentially for 2 minutes each at 10, 20, 30 and 40 mmHg to provide venous occlusion. Blood pressure was measured each minute from the left arm. Continuous multiunit recordings of postganglionic muscle sympathetic nerve activity (MSNA) were obtained via a unipolar tungsten electrode inserted selectively into a muscular branch of the peroneal nerve, posterior to the tibial head. MSNA was quantitated both in terms of burst frequency (burst/min) and burst incidence (bursts/100 cardiac cycle). Two-way (intervention, study day) repeated-measure ANOVA was used for analysis.

Results:

Day	Baseline		10 mmHg	20 mmHg	30 mmHg	40 mmHg	Post
Burst Frequency	1	26.7±7.3	32.6±7.1	32.4±7.4	30.5+9.8	30.6±7.6	27.9±9.6
	2	28.6±9.3	29.5±8.0	32.4±8.3	31.9±10.4	32.3±8.5	30.0±8.1
Burst Incidence	1	41.6±14.6	52.3+16.0	50.5±12.6	48.3±14.3	48.9±15.9	45.5+15.9
	2	46.4±17.9	45.7±13.5	49.8±15.1	50.9±18.3	51.4±16.5	46.7±13.3

* *statistically significant compared to baseline ($p<0.05$).*

Forearm venous occlusion had no effect on heart rate, SBP, DBP or MAP. MSNA was significantly elevated during venous occlusion on both study days, and there was no study day-intervention interaction for MSNA.

Conclusion: Transient increases in venous occlusion pressure cause modest and reversible increases in MSNA. No dose-response relationship was found among different occlusion pressures. Venous congestion may contribute to sympathetic activation in heart failure.

13. MODELLING FUNCTION AND ARCHITECTURE OF SKELETAL MUSCLES IN THE RAT HINDLIMB

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The purpose of this study was to examine and modify a theoretical computerized model of the force-length relationship for a mammalian muscle-tendon complex (Bobbert et al., 1990), and to test this model against experimental data collected from mammalian muscles.

In anesthetized female Wistar rats (250-275 g) the force-length relationships of the fast twitch extensor digitorum longus (EDL, n=4) and slow twitch soleus (SOL, n=4) muscles of the hindlimb were assessed *in vivo*. For each muscle-tendon complex, the distal tendon was cut free from its insertion and connected to a force transducer. To determine the length of the muscle-tendon complexes during contraction, copper wire (0.1 mm diameter) markers were inserted at the proximal and distal end of the proximal aponeurosis and at the distal end of the muscles. Muscle tetanic contractions were generated by electrical nerve stimulation (15 V, 100Hz, 0.2 ms pulse, 400 ms train) and the tetanic force outputs were recorded at different muscle-tendon complex lengths. During the plateau of each contraction, photographs of the complex were taken and then length measurements were determined.

For each muscle, the experimental force-length curve was compared to a theoretical curve predicted by the computerized model. The results showed that the overall shape of the experimental and theoretical curves for either the EDL or the SOL were similar. In general, there was an initial ascending limb at lower complex lengths, a peak or plateau region, and a descending limb at higher complex lengths. In 2 of the 4 EDL muscles, there was good agreement between the experimental and theoretical curves, while in the other 2 EDL muscles the curves generated experimentally were wider than predicted. For the SOL, 3 of the 4 muscles examined demonstrated good fit with the theoretically determined force-length curves while in one muscle the experimental curve was wider than predicted.

It may be concluded that with muscles of simple architecture a good estimation of function is possible in a basic model using few parameters. Such a model can serve as a useful base when introducing additional components to model muscles of increased complexity.

14. FIBRONECTIN SYNTHESIS BY IL-1ß STIMULATED CORONARY MYOCYTES REQUIRES ELASTOLYTIC ACTIVITY

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We have previously demonstrated that the cytokine interleukin-1ß (IL-1ß) upregulates fibronectin (FN) synthesis in subendothelial coronary artery smooth muscle cells (CASMC) of donor hearts following heterotopic heart transplant. Tumor necrosis factor alpha (TNF-α) stimulates endogenous IL-1ß synthesis through a cytokine loop and may synergize with IL-1ß in stimulating FN synthesis. We have also demonstrated that donor CASMC exhibit elevated levels of elastolytic activity believed to be attributable to a 23-kD protein possessing elastolytic activity and characterized as a serine proteinase by its inhibitor profile. We speculate that IL-1ß may modulate the elastolytic activity of endogenous vascular elastase allowing elastolytic products to upregulate CASMC fibronectin synthesis and enhance post-cardiac transplant coronary arteriopathy (PCTCA). In the current study, we investigated the mechanistic involvement of IL-1ß in the synthetic pathway of ^{35}S-methionine labeled CASMC fibronectin, *in vitro*, through the use of serine elastolytic inhibitors. Our results indicate that IL-1ß stimulation of FN synthesis saturates at 300 ng/ml. The serine proteinase inhibitor alpha-1 anti-trypsin inhibits FN synthesis by CASMC in a dose-dependent fashion and shows complete inhibition of the IL-1ß stimulated response at 2.5 mg/ml. Also, the specific elastase inhibitor elafin shows complete inhibition of IL-1ß stimulated FN synthesis to 44% of basal FN synthesis at concentrations of 50 ng/ml and below. Also, interleukin-1ß does not appear to induce elastolytic activity. Elafin inhibition of upregulated elastolytic activity is possible, *in* vivo. These results suggest that IL-1ß stimulation of CASMC FN synthesis in PCTCA requires the presence of basal elastolytic activity, the products of which may acts as stimuli for the synthesis of fibronectin.

15. ESTHESIONEUROBLASTOMA: AN ANALYSIS OF 10 CASES

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Esthesioneuroblastoma is a rare neurogenic tumour of the olfactory epithelium originating from the nasal vault. The authors present the cases of ten patients with esthesioneuroblastoma who were treated between 1980-1994. Data was analyzed with respect to sex, age at presentation, presenting signs and symptoms, treatment and follow-up. Age range was between 17-64 years with a mean of 42.5 years. 9/10 patients received surgery as primary modality of treatment. Surgical approach varied with the time period the patient's presented. 7/10 patients underwent a combined otolaryngological and neurosurgical approach for resection; Two patients underwent a maxillectomy procedure and one patient had no surgical treatment. 9/10 patients underwent adjuvant post-operative radiation therapy with a mean dose of 54 Gy. Two patients in the series recurred, one patient with local metastases to regional lymph nodes and the other with distant metastases. Of the patients that underwent the combined craniofacial resection 6/7 (85%) have remained free of disease. The mean follow up time of patients in this series was 58.3 months. The combined use of craniofacial resection with post-operative radiation therapy seems to be a superior means of treating esthesioneuroblastoma.

16. HAS CYTOLOGY MADE SCINTISCANNING OBSOLETE?

Elizabeth David, Irving B. Rosen, M.D., F.R.C.S.C., Division of General Surgery, Mount Sinai Hospital

Thyroid scintiscanning is considered obsolete by many American authors for surgical selection because of the use of cytology. In 30 patients with "hot" nodules undergoing surgery for incipient hyperthyroidism, 12 had fine needle aspiration biopsies (FNAB) performed and were considered eligible for study. There were 8 females, 4 males with an average age of 46. Seven nodules were autonomous, 5 non-autonomous. Nodule size ranged from 1.5 to 5 cm, with an average of 2.7 cm. Increased thyroid antibodies occurred in 4, familial thyroid problems 2, radiation exposure 2. FNAB showed cancer 1, suspect cancer 8, benign 2, indeterminate 1. Pathology revealed cancer 2 (FNAB colloid 1, suspect 2), occult CA 1 (FNAB benign 1), benign 9 (FNAB CA 1, inadequate 1, suspect 7). Surgery included partial thyroidectomy 7, total thyroidectomy 5 and node sampling 2 without morbidity.

Our conclusions indicate (1) scintiscanning is still essential in detecting the hot nodule whose main concern is primarily for incipient hyperthyroidism and not cancer; (2) FNAB results are unreliable in hot nodules with a predominance of false positive suspect CA FNAB due to benign disease; (3) cancer does occur in hot nodules despite customary belief and its method of detection remains a problem for ongoing study.

17. TREATMENT SELECTION FOR THE "HOT" THYROID NODULE

Elizabeth David, Irving B. Rosen, M.D., F.R.C.S.C., Division of General Surgery, Mount Sinai Hospital

Management of the "hot" thyroid nodule is still poorly defined. Forty-four patients with this condition were treated in the last 3 years with 28 selected for surgery consisting of 22 females, 6 males with an average age of 47. Familial thyroid disease occurred in 5, radiation exposure in 3. Twenty-two nodules were autonomous, 6 non-autonomous. Thyroid function showed euthyroid 12, incipient hyperfunction 10 and definite hyperfunction 6. Surgery consisted of partial thyroidectomy in 20, near-total in 8. Nodules varied from 1 to 5 cm (average of 2.8 cm). There was no postop morbidity. Final pathology showed hyperplasia 18, adenoma 5, papillary cancer 2, follicular cancer 1, Hurthle cell tumour 1, thyroiditis 1. Fine needle biopsy done in 3 cancer patients showed cellularity 2, colloid 1. Fourteen female patients with an average of 62 years were managed non-surgically. Fine needle biopsy done on 5 of the patients showed cellularity in all 5. Nodule size ranged from 1.5 to 3 cm with an average of 2.3 cm. Thirteen nodules were autonomous and 1 was non-autonomous. Eight euthyroid patients were only observed and nodules persisted in all 8 with one patient developing Graves' orbitopathy. Five patients underwent radioiodine therapy producing cold persistent nodules 5 and primary hyperparathyroidism 1. Thyroid suppression in one patient reduced nodule size by 50% but iatrogenic hyperthyroidism after five years compelled discontinuance of therapy.

We conclude that surgery is effective, safe and detects cancer (of surprising frequency in this study) and is definitive where appropriately indicated. Medical management avoids surgery and may be particularly indicated for the elderly and non-compliant patient but bears problems on a long term basis of nodule persistence and treatment side effects.

18. BREAST CARCINOMA WITH MALIGNANT SQUAMOUS DIFFERENTIATION: A RARE HISTOLOGIC VARIANT IN NINETEEN PATIENTS

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The purpose of this study was to determine the clinical, radiologic and pathologic presentation, and to analyze the outcome of treatment in patients (pts) with breast carcinoma with malignant squamous differentiation (MSD). The charts of 19 pts were reviewed to determine clinical presentation, treatment received, and outcome. Histologic sections (19/19) were reviewed by an expert pathologist and mammograms (8/19) by an expert radiologist. A univariate analysis was used to determine the importance of histopathologic tumour features on disease free survival (DFS). Survival curves for overall survival (OS) and DFS were determined using Kaplan Meier estimates.

The median age was 64 years. Eighteen pts presented with a palpable breast mass and 3 with metastatic disease. Mean tumour size was 3.7 cm. Four tumours were cystic, 6 solid, and one had both components. In 12 tumours, the MSD accounted for >50%. The non-squamous component was infiltrating duct carcinoma (ICD) in all cases. Mammograms on 8/8 pts showed a poorly defined mass, only one with malignant calcifications. Lumpectomy was performed in 13 pts and 5 had mastectomy. One pt with Stage IV disease had no surgery. Local recurrence (LR) occurred in 3 of 10 pts who had radiation (RT) and in 4 of 9 who did not have RT> The 5yr OS and DFS were 50% and 20% respectively. Tumour size was the only histopathologic feature of prognostic significance for DFS.

MSD has no characteristic clinical or mammographic feature to distinguish it from IDC. Other than tumour size, there were no apparent histolopathologic features which predicted for DFS. Although the sample size was small, this study suggests that RT may not be as effective in breast carcinoma with MSD.

19. QUALITY OF LIFE (QL) AFTER THE PELVIC POUCH (PP) PROCEDURE

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The PP which eliminates the need for a permanent ileostomy, has been developed to improve QL in patients requiring surgery for ulcerative colitis. The aim of this study was to assess the QL and functional results of patients who had undergone the PP procedure and to determine factors affecting outcome. Of the 653 patients who have a PP, 531 were mailed a 42 item questionnaire. Individuals were excluded if they had had their PP removed, had a defunctioning ileostomy, were lost to follow-up or were deceased. The survey addressed issues concerning stool frequency, urgency and continence as well as diet, appetite, general well being, daily activities and sexual dysfunction. A multivariate analysis was performed using SAS software to assess the effect of factors such as gender, age, weight, medications, pouch and ileo-anal anastomosis (IAA) type on outcome. Three hundred and ninety five (74%) patients returned the questionnaire (210 males and 185 females; mean age 33 years). The mean follow-up time was 4.8 yr. Fifty four percent had less than 6 BMS/d, 66% were continent during the day and 52% at night. Sixty two percent rarely or never had urgency. In 95%, bowel function did not interfere with daily activities. Ninety one percent always or usually felt well, 92% usually or always had a good appetite and 73% had a good energy level always or most of the time. Eighty six percent described their self esteem as good or excellent. Over 90% had no or minimal restrictions in sports, leisure and career activities. Outcome was better in younger patients (P=0.008), those who had S pouches (P=0.006) and had not had an IAA leak (P=0.008). This study showed that functional results and quality of life after the PP procedure are good and that outcome is better in younger patients who have had an S pouch and had not had a leak.

20. THE RELATIONSHIP BETWEEN OSTEOBLAST DIFFERENTIATION AND EXPRESSION OF THE CARBOXYTERMINAL PARATHYROID HORMONE RECEPTOR AND RESPONSE TO HUMAN CARBOXYTERMINAL PTH PEPTIDE 53-84

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This laboratory has been interested for a number of years in the biological effects of carboxyterminal fragments of PTH. Traditional dogma is that all of the physiological actions of PTH are mediated via the amino acid residues within the N-terminal (1-34) region. Two major studies at the lab have shown biological actions for C-terminal PTH and have provided evidence for the existence of a distinct C-terminal PTH receptor on osteoblasts. These findings provided the rationale for this study.

Our purpose was two-fold. First, to study the relationship between osteoblast differentiation and the expression of the C-terminal PTH receptor. Second, to study the relationship between osteoblast differentiation and responses to hPTH (human PTH) 53-84 as measured by alkaline phosphatase activity and osteocalcin production in RCT-1 (preosteoblastic clone) and RCT-3 (mature osteoblastic clone) cells.

Osteoblast cells were grown in 12 well dishes for 7 days then various concentrations of hPTH 53-84 were added for a specified period of time (6 or 24 hours). At the end of the incubation the cells were collected for alkaline phosphatase (ALP) activity assay, and the media saved for an osteocalcin assay. Radioligand binding assays were performed using ^{125}I-Leu^{8},^{18}Tyr^{34}hPTH 1-84.

Binding assays showed that RCT-3 cells appear to have 3-fold higher total number of C-terminal PTH receptors than RCT-1 cells. On the other hand, RCT-1 cells appear to have 3-fold higher osteocalcin production than RCT-3 cells. Also, both RCT-1 and RCT-3 cells appear to show no dose-dependent response to hPTH 53-84 as measured by extracellular osteocalcin concentration levels at incubation periods of 6 and 24 hours. RCT-3 cells appear to have 6-fold higher ALP activity than RCT-1 cells. In addition, RCT-3 cells show maximal stimulation of ALP activity at 10^{-8} M of hPTH 53-84 at 24 hours while RCT-1 cells show no dose-dependent response in ALP activity to hPTH 53-84.

We conclude, first that RCT-3 cells behave as more differentiated osteoblasts compared with RCT-1 cells and second that the human PTH peptide 53-84 stimulates ALP activity in the more differentiated osteoblastic clone (RCT-3) adding further support for the biological role of C-terminal PTH in bone metabolism. The results of the osteocalcin assay are inconclusive and further investigations are needed.

21. CHARACTERIZATION OF THE 5' REGION OF THE MURINE FANCONI ANAEMIA GROUP C GENE

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Fanconi anaemia (FA) is an autosomal recessive disorder characterized by bone marrow failure, congenital malformations, chromosomal instabilities and increased susceptibility to the development of malignancies. FA is a genetically heterogeneous disorder. The FAC gene, defective in group C patients codes for a set of cDNAs that share the same coding region but differ at both 5'and 3' untranslated (UTR) regions. The murine homologue of the FAC gene has been cloned and its 3' region mapped.

Here we report the characterization of the 5' region of the murine FAC gene. A murine genomic library was screened utilizing three different probes previously isolated from the murine FAC cDNA. Twenty two positive phages were isolated. Phages were characterized by Southern blot analysis. From the original 22 phages, 14 hybridized specifically to a probe from the 5' end of the gene, and 4 hybridized to a probe from the middle of the gene. The last 4 phages were complementary to the 3'end of the gene. Blots of partially digested phage DNA were screened with exon specific oligos to determine the order of the fragments.

The restriction map of the 5' end of the murine gene was determined. Preliminary evidence suggests that there is a single 5' UTR exon, possibly dismissing the utilization of two alternative promoters in the mouse gene. Further analysis is required to identify the regulatory sequences of the gene. *(Supported by the Medical Research Council and the Leukaemia Foundation).*

22. AN ANALYSIS OF THE IMPACT OF PUBLIC HEALTH EDUCATION PROGRAMS FOCUSED ON THE PREVENTION OF SCHISTOSOMIASIS IMPLEMENTED IN NORTHERN EGYPT

Dalia Eino 9T7, Supervisors : Colin E. Bayliss, M.D., F.R.C.S.C., Siham Abdul Rihman, M.D.

Schistosomiasis has been endemic in Egypt since Pharaonic times, due to the agricultural and local behaviour patterns which encourage its spread and infection. The infectious agent, a blood fluke, begins its life cycle by egg deposition in the infected host. Some of the eggs are subsequently excreted in the faeces and urine. The eggs hatch and penetrate the intermediate host, the snail. Following maturation the infectious cercariae leave the snail, contaminate waters and penetrate the intact skin of human hosts, where they complete their life cycle. Schistosomiasis infection leads to liver, bladder and lung disease, resulting in high morbidity and mortality. Due to its pathological consequences and high prevalence, schistosomiasis constitutes one of the major health problems of Egypt.

Although the treatment of schistosomiasis is straight forward, the Egyptian Ministry of Health has struggled for many decades to eliminate the disease. Their trials have been unsuccessful due to the heavy dependence of the rural population on canal water, causing recurrent infection and contamination of waters. Recently, the health ministry realized that medical treatment was not sufficient and must be coupled with educational programs to prevent schistosomiasis infection by behaviour modifications. The government launched education programs which were broadcast on television and introduced into schools. These programs described in simple terms the cause, prevention and treatment of schistosomiasis.

The purpose of this study was to analyze the impact which these education programs have had on the population of a small farming village in northern Egypt. The analysis was carried out by correlating collected data from the villagers regarding their knowledge about the cause and prevention of the disease with information regarding their behaviours which put them at risk of becoming infected or contaminating the water, resulting in the infection of others. This information was collected using a verbally administered questionnaire to a randomly chosen set of villagers.

The results showed that although the majority of those involved in the study had correct knowledge regarding the disease, including the mode of infection, transmission and prevention, very few applied this knowledge in modifying their high risk behaviours.

It was concluded that although present education programs have increased the awareness of the population regarding the disease, they have not had a significant impact on modifying their behaviours which result in recurrent infection and contamination of local waters.

23. ADVANCED EPITHELIAL OVARIAN CANCER STUDY

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Purpose: This study was conducted to assess survival and morbidity of treatment in women who presented with advanced epithelial ovarian cancer between 1987-1989.

Methods: A retrospective study was performed of all patients who underwent primary treatment for epithelial ovarian cancer at either Sunnybrook Health Sciences Centre, The Toronto Hospital or The Wellesley Hospital. Eligibility criteria included only patients with suboptimally debulked Stage IIIc (residual tumour diameter > 1cm) or IV disease as determined by the OR note. A datasheet was used to abstract the records of all patients, which were then entered into a computerized database for analysis. Prognostic indicators such as: location of post-operative residual tumour, histologic type and tumour grade were collected. The number of surgical procedures, blood loss, surgical time, post-op stay, and complications were assessed. Planned chemotherapy treatment regimens, drug toxicity and disease status upon completion were also reviewed. Finally, status updates and dates of death were obtained by searching the Cancer Registry of the Ontario Cancer Research and Treatment Foundation.

Results: From the review of 500 charts, there were a total of 160 evaluable patients. The patients underwent an average of 1.7 laparotomies during their course of illness. Primary chemotherapy included a cisplatin-based regimen in 98% of the patients. They received a mean of 2.4 different chemotherapy regimens during the course of their treatment and required a total mean number of 3.9 days in hospital for chemotherapy induced toxicity. The median survival for this group was 20 months and the 5 yr survival was about 10%.

Conclusions: A conservative approach to the management of advanced epithelial ovarian cancer results in an overall low incidence of morbidity within our patient population while achieving survival rates that are comparable with those cited in the literature.

24. ALLOPREGNANOLONE: A MEDIATOR OF PROGESTERONE'S INHIBITORY EFFECTS ON HUMAN TERM MYOMETRIUM?

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Despite intense research efforts the specific mechanisms leading to labour initiation and birth are unknown. Understanding the endocrinology of labour initiation would facilitate the development of safer and more effective procedures for preventing spontaneous preterm labour, and consequently reduce perinatal mortality. This understanding could also aid in the development of safer and more effective labour inducing techniques. Allopregnanolone (3α-hydroxy-5α-pregnane-20-one, AP), one of the principle metabolites of progesterone, may play an important role in the initiation of human labour. It may do so by binding to γ-aminobutyric acid receptors in the uterus and consequently inhibiting uterine muscle contractions up to the time of labour. The experiments were designed to determine the importance of AP in the inhibition of uterine contractions prior to the onset of labour in humans. Levels of AP were measured in maternal serum, fetal serum and amniotic fluid in women who were at the same stage of pregnancy (38-41 weeks). Samples from those who were in labour at the time of sampling were compared with those who were not in labour at the time of sampling. We have established high-performance liquid chromatography and radioimmunoassay systems to separate and measure AP in biological fluid and tissue samples. For patients who where in labour and for those who were not, AP levels were approximately 10% of those of progesterone. Levels of AP in amniotic fluid averaged 20-30% of those in the maternal circulation. These results suggest that AP is present in maternal serum and amniotic fluid at sufficiently high concentrations to potentiate GABAergic transmission. AP biosynthesis may thus contribute significantly to the actions of progesterone in the human myometrium during pregnancy.

25. GLYCEMIA ACUTELY REGULATES METABOLIC GLUCOSE CLEARANCE AT REST AND DURING EXERCISE IN DIABETES

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In moderately insulin deficient diabetes, there is a defect in the muscle's ability to extract glucose from the circulation (glucose metabolic clearance rate=MCR) at rest and during exercise. We have observed a close correlation between glycemia and MCR during exercise which suggests that glycemia *per se* may regulate the muscle's ability to extract glucose. We therefore determined whether acute normalization of glycemia in diabetes, with or without insulin infusion, can regulate MCR at rest and exercise. Experiments were conducted in normal control (C,n=7) and alloxan-diabetic dogs. Diabetic dogs were studied during hyperglycemia (DH,n=6), and during acutely induced normoglycemia (<160 min) with either phlorizin (DP,n=6) (which normalizes glycemia without insulin by increasing glycosuria) or insulin (DI,n=6). MCR (corrected for glycosuria) was determined with 3-^{3}H glucose throughout a 30 min basal period and 60 min of moderate treadmill exercise (100 m/min, 5% slope). Basal glycemia was higher ($p<0.01$) in DH (398±18 mg/dl) than euglycemic groups (C=108±1, DI=104±4, DP=127±6). Basal MCR was significantly lower in DH (0.5±0.1 ml/kg.min) than euglycemic groups (C=2.1±0.1, DI=2.0±0.1, DP=1.5±0.1). During exercise, the increment (Δ) in MCR was lower in DH (0.9±0.1 ml/kg.min) than euglycemic groups (C=3.5±0.3, DI=2.7±0.3, DP=3.0±0.1). Therefore, the acute restoration of euglycemia, with or without insulin, normalized ΔMCR. We conclude that in alloxan-diabetic dogs; the impaired MCR may be an adaptive phenomenon because the acute correction of hyperglycemia, independently of insulin, improves the muscle's ability to extract glucose both at rest and during exercise.

26. FOLIC ACID AND NEURAL TUBE DEFECTS: A RETROSPECTIVE EVALUATION OF PREVENTION AND PUBLIC AWARENESS

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Folic acid, when given periconceptionally, has been proven to prevent up to 75% of neural tube defects (NTDs) ; however, more than half of pregnancies are unplanned and very few women normally consume the necessary 0.4 mcg/d of folic acid.

The purpose of this study was to examine whether Canadian children born with NTDs, who had been conceived at least a year after the preventive effect of folic acid was published, were protected by sufficient amounts of the vitamin and whether their mothers were aware of this important new information.

Twenty mothers whose infants were treated for NTDs at The Hospital for Sick Children in Toronto between January and August 1994 were interviewed and their dietary folate intake assessed by means of a validated food frequency questionnaire.

Mean folate intake of the mothers was 0.193 mg/d ± 0.093 (range 0.02-0.463), less than half the protective dose. Only three mothers (15%) had been aware of the relationship between nutritional folate and NTDs, but even they did not sufficiently supplement themselves. In parallel to the failure of primary prevention of NTDs, there were also common flaws in secondary (diagnostic tests during pregnancy) and tertiary prevention (cesarean section as mode of delivery).

Our study is the first conducted after the causative role of folate in preventing NTDs has been confirmed. It reveals that in one of the most advanced countries in the world, this new information has had little or no impact at the patient level. Unless food fortification with folate takes place, Canada will be unable to prevent its estimated 800 annual cases of NTDs.

27. REFERRAL SOURCE, CARE GIVER AND CLIENT FEEDBACK SURVEYS FOR A COMMUNITY GERIATRIC PSYCHIATRY SERVICE

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This study provided feedback for the Community Psychiatric Services for the Elderly (C.P.S.E.) based on questionnaire responses of Referral Sources and Care Givers and on interview responses of Clients. The feedback was intended to elucidate those functions of the service and its members that were well received and those that may require some review.

42 Referral Sources and 22 Care Givers that had either referred a Client to the C.P.S.E. or had been the primary Care Giver for a referred Client within the past year were mailed a questionnaire. 22 Clients that had been referred to the service within the past year were interviewed. The Referral Sources were randomly selected while the Care Givers and Clients had to meet certain criteria with respect to degree of cognitive impairment and contact with the C.P.S.E.

The questionnaires were largely formulated on the basis of feedback from focus sessions with members of the corresponding populations. Although some questions were generated from within the C.P.S.E. The questions varied from Likert-type (5 point scale) questions to open-ended narrative questions.

The results were tabulated by calculating mean scores and cumulative frequencies for the Likert-type responses and by observing trends within the narrative responses.

The study showed that the C.P.S.E. has been exceptional at catering to those critical issues (care, respect and enabling Clients and Care Givers to play an active role in their care or the care of a client) that were disclosed during focus sessions with Clients and Care Givers. It also showed that issues involving post-referral communication with Referral Sources is an area that may require some review.

28. MAGNETIC RESONANCE IMAGING FOR LOWER LEG ISCHEMIA

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There is a need for a fast, reliable, non-invasive method that can replace X-ray angiography in planning surgical interventions for relief of lower leg ischemia associated with peripheral vascular disease. The utility of current non-invasive methods that rely on flow to generate such information is limited due to the paucity of flow in this application. We have been experimenting with a fundamentally different approach to this challenge termed flow-independent angiography (FIA) using magnetic resonance (MR). The underlying hypothesis is that we can take advantage of the unique characteristics of the MR signal from arterial blood to isolate it from surrounding tissues and then generate a high-resolution projection image of the vasculature. The purpose of this study is to identify protocol issues in a clinical setting to guide the development of FIA using MR. Images of normal and patient volunteers have been obtained using a GE Signa Advantage 1.5T MR imager at the Sunnybrook Health Sciences Centre. Patients were selected from the population seen in the Division of Vascular Surgery at The Toronto Hospital-General Division. All patient volunteers have had X-ray angiography as part of their surgical work up. Images from both groups were reviewed anecdotally to assess vessel conspicuity and overall usefulness for presurgical planning. Images from healthy volunteers revealed the issue of decreased field homogeneity around the foot causing signal variation resulting in decreased image quality. Modifications to positioning techniques were therefore made. More problematic for patient images was the issue of venous suppression, as indicated by initial results, for which elevation of the imaged leg is presently being investigated. For these images, X-ray angiography served as the gold standard. In addition, further suppression of the edema often encountered in this patient population is required. In conclusion, pulse sequence design will be guided by the need for improved venous and edema suppression with the goal of developing FIA using MR into a clinically useful imaging modality.

29. FAMILIAL SEGREGATION OF EXTRAINTESTINAL MANIFESTATIONS OF INFLAMMATORY BOWEL DISEASE: A PEDIGREE ANALYSIS

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Current research trends in the genetics of Inflammatory Bowel Disease (IBD) focus on the familiality of disease characteristics. In an effort to investigate these familial trends, 34 families were identified in which 2 or more family members had been diagnosed with Ulcerative Colitis, (UC) or Crohn's Disease (CD).

The charts of probands and their family members with IBD were reviewed, and probands completed pedigree questionnaires. Information collected included diagnosis, age at diagnosis, and presence or absence of extraintestinal manifestations of IBD. Pedigrees were drawn of the 34 families and linkage analysis was performed.

Analysis revealed that in these families there is a statistically significant increase in the prevalence of IBD compared to the general population. Relatives of UC probands were 2.8 times more likely to have UC, and relatives of CD probands were 10 times more likely to have CD than the general population.

In addition, linear regression analysis of the prevalence of extraintestinal manifestations of IBD in theses families reveals that a family history of extraintestinal manifestations has a significant association with the development of extraintestinal manifestations in another family member ($p= 0.0069$). Neither age nor diagnosis (CD vs. UC) was a significant factor in the development of an extraintestinal manifestation.

In this study , we have initiated the documentation of the prevalence of familial IBD at our institution, and set the stage for the development of a familial IBD registry. In addition, we conclude that CD has a greater familial predisposition than UC, and that extraintestinal manifestations of IBD segregate within IBD families.

30. IMMUNOGENICITY OF ALLOGRAFT VALVED-CONDUITS IN PAEDIATRIC PATIENTS

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Several congenital cardiac defects contain discontinuities between the right-sided ventricle and pulmonary artery. The management of these defects involves the insertion of a valved-conduit to restore continuity. Although allograft, porcine, and other bioprosthetic conduits are currently used, they are consistently plagued by rapid deterioration.

The mechanisms involved in early allograft dysfunction in children remain elusive. Excessive mechanical stress, abnormal calcium metabolism leading to dystrophic calcification, and immunologically-mediated rejection have been postulated. Given the highly polymorphic nature of the HLA histocompatibility loci, it is likely that the vast majority of donor-host pairs are mismatched and susceptible to rejection. This study seeks to determine the pathologic features of allografts removed either at reoperation or autopsy.

From March 5, 1985 through August 28, 1994, 282 children underwent reconstruction of the right ventricular outflow tract using cryopreserved allografts at Toronto's Hospital for Sick Children. In this period, 63 patients required reoperation to explant failed allografts. Clinical, operative, pathology, and autopsy records of these failures were collected and reviewed. Pathological tissue specimens treated with hematoxylin-eosin, Movat, and Gram stains were examined microscopically. Immunoperoxidase staining using T-cell, B-cell, and macrophage-specific antibodies was performed to identify mononuclear inflammatory cells.

Histopathologic features observed in the majority of explanted allografts included calcification, pseudointima formation, degeneration of elastin, and loss of endothelial and deep connective tissue cells in the valvular and arterial wall stroma. Most striking, however, was the presence of mononuclear infiltrates in over 50% of the specimens studied. Numerous lymphocytic aggregates were observed, often localized at the adventitia-media border which corresponds to the donor/recipient interface. A more diffuse infiltration consisting of T-cells was also observed in several specimens. Both the aggregate and diffuse patterns of inflammation were observed in one patient who died secondary to allograft thrombosis. Interestingly, the patient also proved to have high antibody titres reactive versus the donor histocompatibility type.

This study shows that failed HLA-mismatched allografts have the pathological features of chronic cellular rejection. Together, these results suggest a relationship between allograft degeneration, valve failure, and immunogenicity. In turn, a role for HLA-typing or immunosuppressive therapy may be indicated in the future management of allograft recipients.

31. Fe^{2+} UPTAKE IN ISOLATED GUINEA PIG MYOCYTES IS MEDIATED THROUGH VOLTAGE-DEPENDENT CALCIUM CHANNELS

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Cellular iron transport occurs via receptors mediated uptake of plasma transferrin-bound iron and via non-transferrin-bound iron (NTBI) uptake mechanisms. Characterization of the NTBI process has revealed that iron uptake occurs first with the reduction of ferric iron (Fe^{3+}) to the ferrous state (Fe^{2+}). Whole the mechanism of NTBI uptake is currently unknown, uptake requires the reduction of Fe^{3+} to Fe^{2+}. This prerequisite, suggests that NTBI uptake might occur via L-type calcium (Ca^{2+}) channels. To test this hypothesis, we isolated guinea-pig cardiac ventricular myocytes and measured whole cell L-type Ca^{2+} channel currents in the presence of ascorbate reduced iron (Fe^{2+}). In the presence of Fe^{2+} (15-30mM), depolarization to -30 mV to +50 mV from a holding potential of -40 mV, evoked a non-inactivating inward current, blocked by the dyhropyridine nitredipine (10µM). Furthermore, the current-voltage (I-V) relationship was typical of L-type channels, with the peak shifting rightward with increased iron concentrations, as expected for surface charge screening.

Characterization of the mechanism of iron uptake in cardiac cells will help elucidate this process in normal and pathological hearts. In addition, it may be possible to develop therapeutic measures, to modulate iron uptake in iron overloaded states, such as in blood transfused ß-thalassemic patients.

32a. REGULATION OF GENE EXPRESSION IN SMOOTH MUSCLE DIFFERENTIATION FROM EMBRYONIC CELLS

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It is believed that blocking the proliferation of the smooth muscle cell migration in atherosclerosis can block the formation of atherosclerotic plaques. Differentiation of skeletal muscle is regulated by a family of genes including MyoD. Smooth muscle exhibits a pattern of development similar to skeletal muscle and hence this study aims to locate regulatory genes similar to those controlling skeletal muscle development.

This study involves the use of ID - a competitive inhibitor for MyoD which acts by binding to E12 - a protein found in many cell types. ID acts by preventing the binding of MyoD to E12[a ubiquitous protein] and prevents the differentiation of the embryonic cells to skeletal muscle. Thus, we are looking for 1. Smooth muscle cell specific transcription factors and 2. results of overexpression of ID in smooth muscle as in skeletal muscle.

E12 was cloned into an expression vector to form a E12-GST (Glutathione -S- Transferase) fusion protein. The E12-GST fusion proteins were mixed with different nuclear extracts from smooth muscle cells and the final complexes run on an SDS-PAGE gel. To study the overexpression of ID in differentiating smooth muscle cells, the ID protein was transfected into A10 cells (SMC line) with ID downstream to an inducible promoter. The cells were induced at confluence for 3 days, 1 week and 2 weeks. The expression of ID was checked at the RNA level and the protein level through Northern and Western blot analysis.

Preliminary results of SDS-PAGE gel analysis indicate that there are proteins meeting the criteria of MyoD counterparts in smooth muscle in aorta and A7R5 cells. The Id studies have indicated that actin is not present as hypothesized in the induced cells, but is present in the non-induced cells. This finding would indicate that the overexpression of ID prevents smooth muscle cell differentiation, similar to its role in skeletal muscle.

32b. ALTERATIONS IN THE NORMAL PATTERN OF CERVICAL SPINAL CORD MOTION AS MEASURED BY MRI IN SELECTED PATHOLOGIC STATES

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Purpose: To demonstrate how the pattern of normal spinal cord motion is altered by abnormalities of the neural axis.

Materials and Methods: Two dimensional phase subtracted MR imaging sequences were performed in normal volunteers and in patients with abnormalities of the neural axis to assess movement of the spinal cord in relation to the cardiac cycle. Following cardiac systole, 12-22 heart phases at 25-30 msec intervals were collected. Information was calculated by performing phase subtractions on regions of interest within the spinal cord. Data acquisition was performed in the axial or sagittal plane at the level of C3 for all measurements. Duration of the imaging sequences for the study of cord motion was 2-4 minutes.

Results: The cervical spinal cord always moved in a caudal direction during the initial phase of the cardiac cycle reaching a maximum velocity of 6-12 mm/sec between 60 and 140 msec after systole followed by an alternating cranial and caudal motion of progressively decreasing velocity. Patients with spinal cord compression, tethered spinal cord syndrome, and intracranial high flow vascular malformations showed either reduced or increased spinal cord velocities respectively.

Conclusions: The spinal cord clearly moves in an oscillatory pattern following cardiac systole in normal volunteers. Reduced motion occurs in patients with disorders that compress or tether the spinal cord> Increased motion can be seen in patients with intracranial high flow vascular malformations. The ability to assess and grade cord motion may provide clinically useful information in establishing the degree of spinal cord compression or tethering.

33. CLONING AND CHARACTERIZATION OF A NOVEL HUMAN G PROTEIN-COUPLED RECEPTOR GENE WHICH IS EXPRESSED AT HIGH LEVELS IN THE STRIATUM

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In the central nervous system, communication between neurons takes place by the release from presynaptic cells of primary messengers, such as neurotransmitters and neuropeptides, which bind to cell surface receptors on postsynaptic cells. Many primary messengers, including dopamine, serotonin, opioids, and acetylcholine, bind to G protein-coupled receptors (GPCRs) which are a specific class of cell surface receptor. The aim of this study was to identify novel GPCRs in the central nervous system by cloning the genes which encode these receptor proteins.

Our approach involved using degenerate oligonucleotide primers, designed from previously cloned GPCR genes, to amplify human genomic DNA in the polymerase chain reaction (PCR). One unique PCR product was isolated and used as a probe to screen a human genomic DNA library. This resulted in the isolation of a single clone encoding a novel 362 amino acid protein which we named GPR6 and which shared homology to other GPCRs.

Probes containing all or part of the coding region of GPR6 were used to screen: 1) Northern Blots containing human poly(A+) RNA isolated from different brain regions. This revealed an abundance of GPR6 transcripts in the putamen and to a lesser extent in the frontal cortex, hippocampus, and hypothalamus of human brain. 2) Coronal sections of an adult rat brain (in situ hybridization) which revealed an abundance of GPR6 transcripts in the caudate, putamen, nucleus accumbens, and olfactory tubule. Transcripts were also detected in the hypothalamus, hippocampus, cerebral cortex and substantia nigra compacta. 3) Human chromosomal spreads (fluorescent in situ hybridization) which mapped the location of GPR6 to chromosome 6 (q21-q22.1). Experiments to identify the endogenous ligand of this receptor are currently in progress.

The cloning and chromosomal localization of a novel GPCR gene which is strongly expressed in the caudate and putamen will allow us to use this gene as a probe to carry out restriction fragment length polymorphism analysis (RFLP) in the investigation of genetic diseases in which the striatum may be involved such as Tourette's syndrome and schizophrenia.

34. FALLIBILITY AND UNCERTAINTY OF SESTAMIBI SCANNING IN LOCALIZATION OF PATHOLOGICAL GLANDS IN PRIMARY HYPERPARATHYROIDISM (HPT)

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This study examined the value of Sestamibi scanning in pre-operative localization of pathological parathyroid glands. Scans were performed on 40 patients with suspected primary HPT from 1992 to 1994. Thirty-three were female, 7 male. Average age was 61. Average pre-op PTH was 14.8, total calcium (Ca) 2.74, ionized Ca 1.47. Four had recurrent HPT, eleven had a history or thyroid disease. Ten presented with renal symptoms; 14 with GI complaints; 17 with bone disease; 15 with fatigue; 4 with mental changes; 5 with hypertension; 1 with dysphagia and hoarseness; 2 asymptomatic. At surgery, 23 had hyperplasia, 14 solitary adenomas, 1 multiple adenomas, 1 cancer, and 1 was normal. Average post-op PTH was 4.36, total Ca 2.29, ionized Ca 1.25. Pre-operative Sestamibi scans were used to predict the location of hyperfunctioning glands. Among patients with solitary adenomas, scanning correctly localized the pathological gland in 11 cases (sensitivity 79%) although one predicted 3 pathological glands when only one was found at surgery. One patient had 2 adenomas when the scan predicted one. Three scans incorrectly localized the pathological gland. Among patients with hyperplasia, scanning correctly localized at least one pathological gland in 19 cases (sensitivity 82.6%). Eleven of these missed the largest hyperfunctioning gland found at surgery. No scan correctly predicted the location of all pathological glands. There were 4 false negatives. Scanning correctly localized the location of the pathological gland in one patient with parathyroid cancer. Overall sensitivity was 82%. There was one false positive due to a thyroid nodule being mistaken for an adenoma. In the 4 cases of recurrent HPT, scanning correctly localized the pathological gland in 3 cases. One scan correctly predicted the pathological gland to be in the right sub-mandibular region. Scanning was useful in this case in directing surgical exploration to an area which might not have otherwise been searched.

Sestamibi scanning appears to be valuable in the localization of hyperfunctioning glands in patients with recurrent HPT. It has little value in predicting the presence of hyperplasia. Scanning should not be used for diagnosis of HPT because of the potential for thyroid abnormalities to produce false positives.

35. IONIZED CALCIUM DETERMINATION IN ENHANCED DIAGNOSIS OF "EARLY" SYMPTOMATIC PRIMARY HYPERPARATHYROIDISM (HPT)

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There is controversy over what are appropriate indicators for surgical management in the treatment of HPT. It may be common for patients have total calcium levels in the normal range while still suffering from the effects of HTP. Sixty patients with HPT underwent surgical treatment between 1992 and 1994. Average age at surgery was 61.5 (33 to 82). Thirteen patients were male, 47 female and showed recurrent HPT 4, familial HPT 4, thyroid disease 17 (cancer 5, hypothyroid 4, hyperthyroid 1, colloid nodule 1, goiter 2, thyroiditis 4), MEA-11, radiation exposure 6. Twenty-five presented with renal symptoms, 18 with GI symptoms, 22 with bone disease, 22 with hypertension, 1 with dysphagia and hoarseness, 1 vertigo, 1 formicating pain, and 6 were asymptomatic. Ten had undergone cholecystectomy and 6 orthopedic surgery. Average pre-op total calcium (Ca) was 2.77, ionized Ca 1.50, PTH 14.5, chloride (C1) 104.3, phosphate (P) 0.88, ALP 125, random urine Ca 4.1, and C1 to P ration 118. Nine had total Ca levels in the normal range, and 15 had only mildly elevated total Ca (<2.70). One only had a high normal ionized Ca. Of the 24 patients with normal or slightly elevated total Ca, 6 had renal symptoms, 5 had GI complaints, 12 had bone disease, 12 had fatigue, 1 had mental changes, 1 had dysphagia and hoarseness, asymptomatic. Thirty-five patients had hyperplasia, 24 solitary adenomas, 1 multiple adenomas, 2 cancer, 1 normal. No postop morbidity occurred. Postop, average total Ca was 2.31, ionized Ca 1.25, C1 102.4, P 1.11, ALP 105, urine Ca 2.71. Fifty-eight of 59 patients achieved eucalcemia. We conclude that (1) ionized calcium is the preferred screen for HPT; (2) asymptomatic HPT is infrequent; (3) frequency of hyperplasia mandates bilateral approach; (4) low surgical morbidity justifies liberal selection criteria.

36. IVGG TREATMENT OF KAWASAKI DISEASE: ARE ALL BRANDS EQUAL?

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We have previously showed that different preparations of IV gamma-globulin (IVGG) may have different efficacy in preventing coronary artery lesions (CAL) in patients with Kawasaki disease. To address this question further, we reviewed the records of 238 consecutive patients in a single institution with a definite diagnosis of Kawasaki disease between 1985 and 1994.

Treatment regiment and echocardiograms at presentation and at 6-week follow up of the 238 patients were reviewed. 40 patients were not treated with IVGG and were excluded from this study. 30 of the remaining 198 children had CAL at presentation and were analyzed separately. Of the remaining 168 patients, 74 were treated with Brand A (from 7/89-7/91) and 94 were treated with Brand B (from 1/85-6/89 & 7/91 - present). All patients received ASA until the subacute phase. The IVGG preparation were selected on the basis of availability and practice.

There was a statistically significant difference in the proportion of patient developing CAL in the two groups, 20.3% of Brand A as compare to 7.4% of Brand B ($p< 0.05$). Patients in the two groups were similar at initial presentation in terms of their demographic characteristics (sex, age, and days of fever) and laboratory data (initial white blood cell count, bands, platelet, and alpha-1-antitrypsin levels). When the patients treated with Brand B were divided into two groups according to the time they received treatment (from 1/85 to 6/89 vs. 7/91 to present), we found no difference in the proportion of patient developing CAL between these two groups; there was also no difference in the proportion of patient developing CAL between the group treated with Brand A (20.3%) and the group treated with Brand B after 7/91(10.2%). However, there was a statistically significant difference between the group treated with Brand A (20.3%) and the group treated with Brand B before 6/89 (2.9%). Five of 8 patient treated with Brand A and with CAL at presentation had persistence or progression of CAL. Similarly, 11 of 22 patients treated with Brand B with CAL at presentation had persistence or progression of CAL.

Our results suggested that the two brands of IVGG may be different in their effect on CAL development in Kawasaki disease; Brand B was more effective in preventing CAL development than Brand A. The natural history of the disease or perhaps the etiologic agent may have changed during the study period, contributing to the difference in effectiveness of Brand B at the different times.

37. ALTERNATIVE STRATEGIES FOR PROCESSING MAGNETIC RESONANCE IMAGES TO EVALUATE BRAIN FUNCTION

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Recently, there has been much interest in using MRI to assess functional activation of the brain. However, image acquisition protocols currently in use may be sub-optimal. The purpose of this study is to improve the protocol for functional MR so as to show accurate cortical activation without the introduction of extra "noise". It is hypothesized that during the scanning period, the blood flow response to the brain changes and therefore not all of the images acquired during a scanning period will be similar, as is currently thought.

The basis of functional MR is the increase in cortical blood flow that results from the application of a repeated stimulus. The increased flow can be detected by MRI because of the different magnetic properties of flowing, oxygenated blood. In this study, six MR images in the "off" (no stimulus) state are taken, followed by a series of six "ons" (stimulus present) of one intensity, then followed by another series of six "ons" of a different intensity. This sequence is then repeated six times, producing 108 images. An image acquisition time of six seconds was chosen to achieve high spatial resolution. Comparison of a mean "on" and a mean "off" image yielded a difference image, which was subjected to a pixel-by-pixel t-test. Pixels which showed a significant difference between "on" and "off" (p value <0.01) were arbitrarily assigned a high intensity value, so as to appear bright and thereby producing an activation map. These maps were subsequently processed to determine if the areas of activation yielded any reliable information about the functional status of the brain. Reprocessing of the data using different parameters was done to determine if there were any systematic errors that could be eliminated, to increase the accuracy of the procedure.

This study showed several preliminary findings. First, for a particular stimulus, changing the intensity of the stimulus did not alter the activation map produced. However, the absolute difference between the "on" and "off" state in the high intensity stimulus was greater than that for the low intensity stimulus. Second, the cortical response as shown by MRI changed as the sequence of 108 images was acquired. Third, when the image intensities were plotted, it was shown that the first image from every group of six had a higher intensity than the rest. From this study, we can conclude that the current protocol being used for functional MRI studies of the brain are not optimal and that modifications can be made to improve the method of data acquisition and data processing.

38. THE EFFICACY OF A COMPUTER-ASSISTED PRE-OPERATIVE TUTORIAL: A PILOT STUDY

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One major difficulty for medical school faculties is to educate students from diverse backgrounds efficiently and effectively with little opportunity for individualized attention. Recognizing the need for change in both the substance and style of medical education, the Panel on the General Professional Education of the Physician of the Association of American Medical Colleges suggested that medical schools should lead in the application of computer technology and promote their effective use . The purpose of this study was to investigate the efficacy of a pre-operative computer-assisted tutorial in helping clinical clerks understand the anatomy of operative procedures they were about to participate in.

The study sample consisted of eight fourth-year clinical clerks during their 8-week surgery rotation at the Toronto Hospital (General Division). A repeated measures experimental design was used. For the experimental condition, each subject received a tutorial on the anatomy of the operative procedure before entering the operation. For the control condition, subjects received no intervention. Each subject observed a different operative procedure for the experimental and control conditions. Order of baseline and experimental conditions was counterbalanced across subjects. Following the completion of an operation, each subject filled out a 8-item questionnaire regarding their experience in the O.R. and the most senior surgeon present throughout each operation filled out a 6-item questionnaire regarding the clerk's performance in answering anatomical questions relevant to the operation. Each question on the questionnaire was answered using a 5-point Likert scale. Scores on control and experimental questionnaires were compared using a 1-tailed t-test.

Analysis showed a significant increase in scores on the student questionnaires for operations preceded by an tutorial compared to scores for operations without a tutorial ($\Delta = 7.29 \pm 4.19$, $t(7) = 4.92$, $p<0.001$). Similarly, there was a significant increase in the scores on surgeon evaluations of the clerks for operations preceded by a tutorial compared to operations without a tutorial ($\Delta = 4.57 \pm 3.14$, $t(7) = 3.57$, $p<0.01$).

The results of this study suggest that a pre-operative tutorial consisting of computer-based instruction complemented by a human instructor is effective in teaching clinical clerks the anatomy of surgical operations they are about to participate in. These results also suggest that students feel more confident and prepared concerning the anatomy of an operation after receiving the tutorial. We conclude that sufficient evidence is present to proceed with further research which would determine whether a tutorial using the computer alone would have a similar benefit.

39. ANALYSIS OF GENE EXPRESSION PATTERNS IN ADULT AND FETAL HUMAN HEARTS BY EXPRESSED SEQUENCE TAGS (ESTS)

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Cardiac development is a complex process involving simultaneous and concerted expression of thousands of genes. While many studies have attempted to understand the roles of small numbers of genes in this intricate process, few studies have characterized large scale gene expression in the developing heart. This study therefore endeavoured to identify and classify genes expressed in cardiac development, and to understand how and why this expression differed from that observed in the mature (adult) heart.

To identify genes expressed in the developing heart, a cDNA library representing all expressed genes was constructed from fetal hearts (12 weeks gestation). Clones from the cDNA library, each representing one specific gene transcript, were sampled at random and used for DNA sequencing to produce expressed sequence tags (ESTs). These ESTs were compared against all known gene sequences in the Genbank database, in order to establish the identity to the clone.

Over 5500 ESTs from adult and fetal heart cDNA libraries have been generated to date. Of these, 520 adult and over 450 fetal ESTs corresponding to known genes were classified into 10 categories according to function. Comparison of ESTs in each category demonstrated a much higher proportion of gene transcripts dedicated to contractile functions in the adult heart than in the fetal heart. On the other hand, the fetal heart exhibited more transcripts devoted to signal transduction and cell regulation and to protein synthesis than did the adult heart--perhaps indicative of the rapidly growing, relatively less differentiated state of the fetal heart. Similar comparison of cardiac gene expression with other tissues demonstrated correlation of gene expression with structure and function of the tissues.

Sequencing of cDNA clones to generate ESTs is therefore an effective means of examining gene expression on a large scale in the developing heart, and of understanding how this expression impacts upon the structure and function of the growing heart.

40. ROLE OF CYTOKINES IN THE REGENERATION OF THE STRATUM CORNEUM

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Over the past several decades it has become clear that keratinocytes are a potent source of cytokines and growth factors. These play a role in normal homeostatic mechanisms and in repair mechanism. Minor trauma to the skin can result in disruption of the outermost layer, the stratum corneum. This study was undertaken to evaluate the effect of minor trauma to the skin on the generation of epidermal cytokines. Normal volunteers were subjected to minor trauma to the forearms using repeated applications of cellophane tape. Biopsies from the tape stripped areas were taken at 0, 1, 2, 4, and 7 days post tape stripping. RNA was extracted from the biopsies and was reversed transcribed to make cDNA which was then amplified using specific cytokine primers. The cytokines evaluated were Interluken 1 (IL-1) Tumour necrosis factor alpha (TNF*a*) Keratinocyte growth factor (KGF) and Transforming growth factor beta. The results of this study showed that these cytokines were up-regulated following injury and then returned to basal levels as the skin regenerated. The results of this study suggest that keratinocyte cytokines may be involved in the wound healing phenomena at an earlier time point (day 4).

41. PRIOR DIAGNOSIS AND TREATMENT OF PATIENTS REFERRED TO AN ASTHMA CENTRE WITH A SUBSEQUENT NEGATIVE METHACHOLINE CHALLENGE STUDY

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Previous research indicates that asthma has been underdiagnosed. However, we suspect that such widespread attention to the underdiagnosis of asthma has lead to an overdiagnosis of asthma in many cases. We therefore sought to examine prior diagnosis and treatment of patients referred to our facility and subsequently shown to have no objective evidence of variable airflow limitation. We retrospectively reviewed the charts of 176 patients referred to us who had normal spirometry and a negative methacholine challenge (PC_{20}>8mg/ml). A prior diagnosis of asthma or possible asthma was indicated in 129 patients (73%) by referring physicians. Sixty-two percent (109) of the patients were previously treated with at least one asthma medication. The mean duration of treatment was 25.9±56.3 months. Of those treated, 89 (82%) received inhaled B2-agonists, 66 (61%) received inhaled corticosteroids, 18 (17%) received at least one course of oral corticosteroids, 20 (18%) received oral bronchodilators, 16 (15%) received an inhaled nonsteroid antiinflammatory and 14 (13%) received ipratroprium bromide. Approximately 38% received one class of medications only, 355 received 2 classes, 17% received 3, and 9% received 4 or more types of medications. The diagnosis following referral and investigation were as follows: bronchitis/rhinitis/allergic rhinitis - 64, no specific diagnosis mentioned (not asthma) - 45, asthma/possible asthma (despite -ve challenge) - 22, deconditioning/obesity/hyperventilation syndrome/adductor spasm - 15, post viral cough syndrome - 9, COPD - 6, other - 15. Considering the psychological implications, cost to individuals and potential for side effects from medications, primary care physicians should liberally use challenge studies and possibly referrals to specialists when the diagnosis of asthma is not certain.

42. THE EFFECT OF A SITTING VERSUS LYING POSITION ON SACRAL TRANSCUTANEOUS OXYGEN PRESSURES IN SPINAL CORD INJURED INDIVIDUALS

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Pressure sores are a common complication following spinal cord injury (SCI). One important factor influencing wound healing is the adequacy of tissue oxygenation in the ulcerated area. The purpose of this study is to determine the effect of a position change, from lying to sitting, on sacral transcutaneous oxygen pressures in SCI individuals.

Oxygen pressures at the sacrum were measured in 20 individuals with SCI (7 quadriplegics and 13 paraplegics) and 9 able-bodied subjects in both the recumbent and sitting position using a transcutaneous oxygen monitor (Model 840, Novametrix Medical Systems). Complete pressure relief was maintained over the sacrum in both positions. The results showed that there was a significant increase in transcutaneous oxygen pressures (TcO_2) from the lying to the sitting position in the able-bodied group (37.39±7.66 mmHg in lying, 50.16±7.90 mmHg in sitting, p=.02), as well as in the SCI group (31.58±11.64 mmHg in lying, 41.28±13.44 mmHg in sitting, p=.008). It was noted, however, that there was considerable variability in TcO_2 values within the SCI group as compared to the able-bodied group. The coefficient of variation (CV) was 36.3% and 32.6% in the SCI group versus 20.5% and 15.8% in the control group in lying and sitting respectively. When the SCI group was divided into quadriplegics and paraplegics, the quadriplegic group showed no significant difference between lying and sitting TcO_2 values (30.47±4.01 mmHg in lying, 40.74 ±13.14 mmHg in sitting, p=.13) whereas in the paraplegic subgroup, a significant difference was found between the two positions (32.18±14.11 mmHg in lying, 41.56±14.12 mmHg in sitting, p=.04).

These data demonstrate that there is a significant difference in the sacral TcO_2 in the two positions among the SCI individuals. It would therefore appear that a sitting position which maintains complete pressure relief over the sacrum will not compromise oxygenation of sacral tissue in SCI individuals.

43. IS THE MAYO MODEL FOR PREDICTING SURVIVAL USEFUL FOLLOWING THE INTRODUCTION OF URSODEOXYCHOLIC ACID TREATMENT FOR PRIMARY BILIARY CIRRHOSIS?

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Treatment of patients with primary biliary cirrhosis (PBC) with ursodeoxycholic acid (UDCA) leads to a marked reduction in serum bilirubin. The first objective of this study was to assess the validity of certain prognostic indicators for PBC after treatment with UDCA. Serum bilirubin is an important prognostic indicator for PBC and an important component of the Mayo model for predicting survival in these patients. In an analysis of patients enrolled in the Canadian multicenter trial, the Mayo score was calculated before and after treatment with UDCA. After treatment, the Mayo score continued to predict survival in patients with PBC. In addition, the serum bilirubin alone was shown to be a predictor of outcome even after treatment with UDCA. A second objective was to establish whether UDCA had an effect on long-term (2-6 years) survival in patients with PBC. The difference in survival between those patients initially randomized to UDCA and those patients randomized to placebo was not statistically significant. This study shows that the Mayo model can be used to time liver transplants in patients with PBC who have been treated with UDCA, but more research must be done to establish a definite survival advantage from treatment with UDCA for PBC.

44. THE DISTRIBUTION OF PROSTAGLANDIN SYNTHASE IN EMBRYONIC TISSUES IN RELATION TO ITS POSSIBLE ROLE IN BIOACTIVATING THE ANTICONVULSANT DIPHENYLHYDANTOIN

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Exposure to the anticonvulsant diphenylhydantoin (dph) during pregnancy has been associated with a variety of birth defects known as the fetal hydantoin syndrome. Recent evidence suggests that dph may be bioactivated in embryonic tissues by prostaglandin synthase (pgs) to a free radical reactive intermediate which if not detoxified may attack essential macromolecules, thereby initiating teratogenesis and embryotoxicity. This has lead to the hypothesis that the embryonic tissues susceptible to the teratogenic effects of dph are those expressing the enzyme during the critical period for dph-induced teratogenicity. In order to test this hypothesis, the expression of pgs was studied by indirect immunohistochemistry at various stages in development of mouse embryos using a polyclonal antibody to pgs.

Serial sections of neutral buffered formalin-fixed embryos were treated with a 1:200 dilution of goat anti-pgs. The antibody was localized with biotinylated rabbit anti-goat IgG and avidin-conjugated horseradish peroxidase. Specific immunostaining was identified using 3,3' diamino-benzidine as the chromogen. Binding of the pgs antibody was observed in the extraembryonic membranes, heart, neural tube, somites, kidney tubules and endoderm. The pattern and amount of binding changed with the stage of development. The binding observed in the heart is consistent with reports of cardiovascular malformations induced in embryos by dph treatment of pregnant mice. However, the absence of immunohistochemically detectable levels of pgs in the limb buds and palate, the structures most frequently affected in the murine hydantoin syndrome, suggests that the putative pgs-generated reactive intermediate is transported to these tissues from other embryonic sites. The results also imply that the tissues affected by the teratogen lack critical pathways for detoxification and cytoprotection during the critical period for dph-induced malformation.

45. HEALTH STATUS AND LIFE EXPERIENCES OF STREET-INVOLVED YOUTH IN THE CITY OF TORONTO

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Street-involved youth are diverse and have unique health needs which are often missed through traditional population-based studies. Over the last 5 years, U of T medical students have implemented a longitudinal study of the health needs of this high-risk group. Recent studies in Toronto identified important health concerns unique to adults living on the streets. Youth living on the streets are exposed to many of the same health risks. In light of the past U of T studies and the recent literature from other Toronto based organizations, the health status, access to health care and risk factors of street-involved youth was examined to identify changing trends and emerging needs.

A survey was developed in consultation with numerous community agencies to determine demographics, education, source of income, use of services, family history, history of abuse, drug and alcohol use, sexual history, chronic and periodic health concerns, use of medical professionals, barriers to access and mental health status of street involved youth. One hundred youth, from six community agencies were interviewed. Attempts were made to include a significant number of youth with Native heritage (25%) and youth who participate in the sex trade (33%).

The average age of the youth interviewed was 19.5. Almost half (47%) of the youth had been street-involved for more than 2 years. As children, the youth had experienced high levels of abuse (80%) and 47% had been in protective custody at least once. Over the last five years, three health clinics in downtown Toronto have been developed to meet the specific needs of street youth. The data suggest that the youth are using these services; 90% of the youth have seen a doctor in the last year. As was seen in homeless adults allergies, asthma, head injuries, epilepsy and joint pain are common chronic concerns for these youth. In the last six months headaches, fatigue, colds and weight changes have been the most common and most serious problems for the youth. Almost all of the sample (94%) had been sexually active in the last year and although knowledge about HIV and STDs was high condom use was generally low. Youth were found to have high levels of depression and psychotic thoughts and low self esteem.

In conclusion, health clinics are increasing the accessibility of health care to this high risk population. Despite this improvement, street-involved youth continue to suffer from the effects of abusive childhoods, mental health problems and the risks inherent in street life.

46. ROLE OF OXIDIZED LIPOPROTEINS IN RENAL FIBROSIS

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A number of studies have shown evidence that progressive fibrosis of the tubulointerstitium is the final common pathway leading to end-stage renal failure, regardless of the original cause of renal disease. Other studies have suggested that macrophages, recruited to the interstitium, release cytokines, which then stimulate interstitial fibroblasts to secrete matrix proteins. Although the mechanisms that trigger cytokine-release remain to be elucidated, parallels between atherogenesis and renal fibrosis have lead to speculation that lipids may be involved. As in atherosclerosis, the oxidation and subsequent uptake of oxidized low density lipoproteins (OxLDL) by macrophages may play critical roles in the initiation of renal fibrosis. Thus the purpose of this pilot-study was to further elucidate the role of oxidized lipoproteins in renal fibrosis.

Nephrotic syndrome was induced in rats by a single injection of puromycin aminonucleoside (PAN). Experimental animals received either lovastatin (an HMG-CoA-reductase-inhibitor) or probucol (an antioxidant), while control rats were injected with either PAN alone or with saline. Kidneys were harvested at 7, 14, and 21 days. Total RNA was isolated and analyzed by Northern blot, using ^{32}P dCTP labeled cDNA probes for fibrogenic cytokines. mRNA signals on autoradiographs were quantitated by laser densitometry and adjusted for unequal RNA loading. Results were analyzed using Bonferroni's t-test.

	Control	PAN alone	PAN + probucol	PAN + lovastatin
TGF-ß1				
Week 1:	100%	290%	170%*	260%
M-CSF				
Wk 1:	100%	440%	157%	467%
Wk 2:	100%	160%	98%	170%
Urinary albumin mg/100g B.W.				
Wk 1:	0.2 ± 0.1	300 ± 43	304 ± 45	274 ± 40
Wk 2:	0.4 ± 0.3	260 ± 83	115 ± 56*	160 ± 110

*p<0.05, Bonferonni's t-test, compared to animals with PAN alone.

Assessment of mRNA levels for other matrix-encoding genes and total kidney collagen content are currently in progress. mRNA levels of TNF-α and fibronectin, a matrix proteins, were also measured and found to be unchanged between the experimental groups.

This pilot-study demonstrated that PAN-induced nephrosis caused an elevation of TGF-ß1 mRNA levels that was markedly attenuated by probucol. A similar trend, though not quite statistically significant, was observed for M-CSF mRNA. Nevertheless, we believe that the findings suggest a trend that should be borne out in subsequent larger experiments. These findings suggest that probucol, perhaps through its antioxidant properties, may be acting to prevent macrophage activation and subsequent release of fibrogenic cytokines in PAN-induced nephrosis. Further work with a larger number of animals is planned to validate these preliminary findings.

47. REGULATION AND EXPRESSION OF MDR GENES IN THE INTESTINAL EPITHELIUM

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The MDR genes are highly conserved membrane glycoproteins whose over-expression mediates the multi-drug resistant phenotype in a variety of tumours. The intestinal epithelium is one of the few normal tissues which express mdr genes at high levels. Of the three rodent mdr genes, only mdr1 expression has been reported in the intestine. To identify the DNA elements regulating intestine-specific mdr expression, a series of hamster mdr1 a promoter deletions were mapped in the rat intestinal epithelial cell line, IEC-18. Intestine-specific enhancer (-100 to -52) and repressor (-299 to -254) regions were identified, each conferring a 12-13 fold effect on promoter activity. Northern blotting demonstrated a low level of mdr1a transcript in IEC-18 and a surprisingly high level of mdr1b. . The hamster mdr1b promoter did not exhibit significant activity in these cells. Quantitative RT-PCR was used to assess the relative expression levels of the mdr genes in IEC-18 cells, as well as along the proximal-distal and cryptvillus axes of the intestine. Preliminary results indicate an anomolous over-expression of mdr1b in IEC-18 compared to primary intestinal epithelium. We have identified intestine-specific mdr1a promoter elements, the presence of mdr1b and quantitative mdr gene-specific expression patterns in the intestine.

48. USE OF 7-DIETHYLAMINO-3(4'-MALEIMIDYL-PHENYL)-4-METHYLCOUMARIN (CPM) IN LABELLING THE KIDNEY NA+/D-GLUCOSE TRANSPORTER

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Fluorescent amino group specific reagents can be used to label the Na^+/D-glucose cotransporter (SGLT1) in intestinal brush border membrane vesicles (BBMV) (Am. J. Physiol. 264:G300, 1993). In kidney BBMV, Na^+-dependent glucose transport is believed to be mediated by a protein identical to SGLT1 and also a low affinity Na^+/D-glucose cotransporter (Biochim. Biophys. Acta 1153:43, 1993). The purpose of the present study was to label the Na^+/d-glucose cotransporters in kidney BBMV with fluorescent sulfhydryl group specific reagents. To reduce non-specific labelling, BBMV prepared from dog kidney cortex were pretreated with N-ethylmaleimide (NEM) and N-(3-pyrene)maleimide in the presence of 100 mM NaCl and 5 uM of the Na^+/D-glucose cotransporter inhibitor phlorizin. These vesicles were then treated with CPM, a fluorescent sulfhydryl group specific reagent, in the presence of 100 mM NaCl. By monitoring the increase in CPM fluorescence at 475 nm, we observed that a component of the CPM labelling was inhibited by addition of 5 uM phlorizin. Using ^{3}H-phlorizin, each of the maleimides were shown to inhibit high affinity Na^+-dependent phlorizin binding in an irreversible but phlorizin protectable manner. These results suggest that the Na^+/D-glucose cotransporters in kidney BBMV can be labeled with CPM. Thus, CPM may prove to be a useful probe in studying the conformational dynamics of the Na^+/D-glucose transporter and the differences in Na^+-dependent glucose transport in the kidney and intestine.

49. NEW SERUM MARKERS FOR ACUTE MYOCARDIAL INFARCTION

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Standard laboratory markers such as CK and CK-MB continue to play a major role in the triage and diagnosis of acute myocardial infarction (AMI) in the emergency room. However, there are new and reportedly more specific, protein markers such as myoglobin, troponin and myosin light chains. Each marker exhibits a time-dependent change and their effective use in combination to triage and diagnose AMI requires careful optimization for maximum efficiency in the detection of early and late presenting cases.

This study reviewed the current literature on serum markers, profiled the use of current markers and assessed the potential of newer markers in AMI. Patients presenting with chest pain to the emergency room were included. Data was collected on a standard form and included demographics, signs and symptoms, ECG findings, medications, serum marker levels, discharge placement and discharge diagnosis.

Forty-eight patients were included in the study of which 15% had documented AMI on discharge. The study suggests a role for myoglobin as an early marker of AMI and a powerful member of a tandem of AMI serum markers. Data regarding troponin were unavailable at the time of submission.

50. ATRIAL ARRHYTHMIAS IN ADULT PATIENTS TWO DECADES AFTER REPAIR OF TETRALOGY OF FALLOT

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The importance of atrial tachyarrhythmias (AT) in adults late after repair of Tetralogy of Fallot (TOF) has not previously been recognized. Repaired TOF adults assessed since Jan 1990, were reviewed to determine the prevalence, and prognosis of AT and ventricular tachycardia (VT) late after repair of TOF.

Results. A history of symptomatic sustained AT as a presenting arrhythmia was found in 17 pts, and a history of documented sustained VT in 12 pts. Clinical features were compared to 157 pts who comprise the non-arrhythmia (NA) group. One patient with AT and VT at presentation was excluded.

	AT	VT	NA
Age at Repair (yrs)	22.7 +/- 15.1 *	10.7 +/- 12.8	11.3 +/- 10.5
Age Arrhythmia Onset	38.4 +/- 11.5 #	25.8 +/- 9.6	
Age at Last Visit (yrs)	45.0 +/- 10.6 *	31.6 +/- 10.6	30.3 +/- 10.3
LV Ejection Fraction	57.1 +/- 11.9 •	54.1 +/- 11.5	55.8 +/- 10.9
RV Ejection Fraction	40.9 +/- 19.2 •	34.1 +/- 8.3	38.7 +/- 11.1

* $p < 0.001$ # $p < 0.005$ • Not Significant

At onset of arrhythmia, heart failure was present in 7 AT pts but no VT pts. In follow-up 2 of 17 pts (12%) with AT have died (1 developed right heart failure and VT prior to death), compared to 1 of 12 (8.3%) in the VT group and 5 of 157 (3.2%) in the NA group. Among the surviving AT pts, 3 are in chronic atrial fibrillation and 1 paced. Two pts were on no arrhythmia therapy, 8 were on digoxin (1 also on Sotalol), 5 pts not on digoxin were on Quinidine (1), Sotalol (2), or Amiodarone (2). Surviving AT pts were more likely to be treated with ACE inhibitors or diuretics (47% vs 8% vs 7% for AT vs VT vs NA).

Conclusion. AT is an important problem in adult TOF pts. AT pts are older at initial repair, and at follow-up. Pts with AT are more likely to present in heart failure, and are more likely to require continuing therapy for heart failure, than the VT or NA groups.

51. INITIAL HUMAN EXPERIENCE WITH ADENOSINE SUPPLEMENTED CARDIOPLEGIA

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Present techniques of myocardial protection during isolated coronary artery bypass graft (CABG) surgery still result in intraoperative myocardial damage. There is evidence that adenosine is cardioprotective in different animal models, however, administration of adenosine, in humans, may be limited by hypotension and heart block. The purpose of this phase 1 study was to determine a safe dose of adenosine in humans using two different cardioplegic formulations.

Patients undergoing isolated CABG surgery were eligible. The study was open and nonrandomized, and was conducted with two cardioplegia mixtures. The first used a 4:1 blood:crystalloid solution. The adenosine doses tested were, 1, 2.5, 5, 10, 25 and 50 µmol/L. These doses were tested sequentially. Based on the results of the 4:1 cardioplegia group, adenosine doses of 15, 20 and 25 µmol/L were used in a group of patients receiving an 8:1 blood: crystalloid cardioplegia. The end points of the study were: 1) hypotension, defined as total phenylephrine administration of ≥ 5.0 mg during cardiopulmonary bypass or ≥ 800 mg during initial cardioplegic induction, and 2) AV block, defined as permanent pacemaker dependency, or temporary pacemaker dependency for ≥ 90 minutes (resting heart rate < 50 bpm).

There were no deaths, Q-wave myocardial infarctions, intra-aortic balloon pump insertions, nor cerebrovascular accidents. The results of the study with respect to hypotension are provided in table 1. In the 4:1 cardioplegia group, an adenosine dose of 50 µmol/L was associated with an increased incidence of hypotension ($p < 0.05$). In the 8:1 cardioplegia group, an adenosine dose of 25 µmol/L was associated with an increased risk of hypotension ($p < 0.05$), and there appeared to be a threshold effect at a dose of 20 µmol/L.

Blood:Crystalloid	4:1	4:1	4:1	4:1	4:1	4:1	4:1	8:1	8:1	8:1
Dose	0	1	2.5	5	10	25	50	15	20	25
n	4	4	4	4	4	4	4	8	8	4
Total Phenylephrine (mg)	2.0 ± 2.7	1.5 ± 0.6	1.7 ± 2.0	1.3 ± 1.2	1.4 ± 0.7	1.8 ± 1.5	3.0 ± 3.4	1.5 ± 1.0	1.1 ± 1.2	1.1 ± 1.2
Total Phenylephrine ≥ 5 mg (n)	1 / 4	0 / 4	0 / 4	0 / 4	0 / 4	0 / 4	0 / 4	0 / 8	0 / 8	0 / 4
Initial Phenylephrine (µg)	280 ± 281	300 ± 101	440 ± 604	240 ± 339	260 ± 120	260 ± 77	880 ± 217	421 ± 200	360 ± 355	600 ± 477
Initial Phenylephrine ≥ 800 µg (n)	0 / 4	0 / 4	1 / 4	0 / 4	0 / 4	0 / 4	3 / 4	1 / 8	2 / 8	2 / 4

Table 1: Hypotension. Values are mean ± standard deviation.

There was one patient who required temporary pacing for 90 minutes in the 50 mmol/L dose in the 4:1 cardioplegia group. No other patient required pacing for ≥ 90 minutes nor did any patient require permanent pacing. Thus, the use of adenosine as an adjunct to warm blood cardioplegia during CABG appears to be safe. It is recommended that further studies with adenosine be done at a dose of 15 - 25 µmol/L, with the precise dose depending upon the cardioplegic formulation.

52. HEPATITIS C FOLLOWING LIVER TRANSPLANTION

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Since testing for Hepatitis C Virus (HCV) became available in 1991, HCV has become the most common indication for liver transplantion. The natural history of recurrent HCV remains unclear.

A retrospective analysis of the first 391 liver transplants in 361 adult patients was done. Patients transplanted for Non-A Non-B viral hepatitis or cryptogenic cirrhosis (n=67) prior to 1991, and those who were HCV +ve preop (n=29) were analyzed. 29 of the 67 Non-A Non-B and cryptogenic patients, and 29 of the 29 preop HCV +ve patients were tested for HCV postop. 21 of 29 Non-A Non-B or cryptogenic cirrhosis patients had test results completed; 9 (43%) were HCV +ve postop. 26 of 29 HCV +ve patients had test results completed where 25 (96%) were HCV +ve postop. 33 of 34 postop HCV +ve patients were analyzed. Recurrent HCV disease was defined as positive serology with increased liver enzymes (fluctuating), histology compatible with HCV hepatitis, and failure to respond to anti-rejection therapy. In 12 (36%), there was no evidence of recurrent disease in the liver graft. These 12 patients were 128 to 1604 days posttransplant (mean=612, median=477 days). In the other 21 (64%), HCV disease recurred from 17 to 1670 days (mean=228, median=132) posttransplant. 12 (57%) recurred within the first four months and 6 (29%) recurred after the first year. The severity was mild (AST<150IU/ml, no symptoms) in 11 (52%), moderate (AST>150IU/ml, mild symptoms) in 1 (5%), and severe (requiring Ribavirin therapy) in 9 (43%). Severity appeared to correlate with time to recurrence with 8 (89%), of the 9 with severe disease, recurring within the first four months. Initial histology ranged from mild and difficult to differentiate from acute rejection to severe disease with dense lymphocytic aggregates and hepatocellular necrosis. Serial histology was available in 8 patients; 4 progressed to fibrosis within 0 to 271 days following recurrent HCV. All 9 patients treated with Ribavirin responded with a fall in liver transaminases within one month, which continued during the duration of the drug.

In conclusion, recurrent HCV may be difficult to distinguish from acute rejection. Two-thirds who are HCV +ve postop develop HCV disease. Early recurrence is associated with increased severity. Initial experience with Ribavirin is encouraging and deserves further study. The long term sequelae of recurrent HCV remain to be determined.

53. INTEGRIN SUBUNIT EXPRESSION IN HUMAN GLIOMA CELL LINES

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Integrins are a superfamily of glycoproteins which are the major mediators of cell/extracellular matrix (ECM) interactions. Integrins are heterodimeric proteins composed of an α and ß subunit. Each subunit contains a transmembrane domain allowing the integrin molecule to span the plasma membrane. The cytoplasmic portion binds a variety of cytoskeletal proteins, while the extracellular domains bind ECM proteins. Processes such as cell adhesion, migration, differentiation and growth are all dependent upon interactions between the ECM and the cell. Therefore it is not surprising that derangements of integrin expression have been reported in a variety of human cancers. Previous qualitative studies of glioma cell lines have demonstrated some alterations in integrin expression. This study examines integrin subunit mRNA expression in seven glioma cell lines, using semi-quantitative methods.

RNA was extracted from each cell line. A reverse transcription reaction was employed to generate cDNA using an integrin subunit and ß-actin primer. The cDNA was amplified by PCR, and samples were aliquoted from the PCR reaction after 20, 25 and 30 cycles. Samples were separated by agarose gel electrophoresis, photographed and analyzed by densitometry. Results were expressed as the ratio of the integrin band intensity over the internal control (ß-actin) band intensity.

This study demonstrated that expression of integrin subunit mRNA in all of the glioma cell lines clearly deviated from that which would be expected in a normal astrocyte. Specific integrin subunit mRNAs (α3 and ß4) were shown to be overexpressed in the majority of cell lines. Finally, a considerable variation in integrin mRNA subunit expression was found between each cell line. Further study will be directed towards verifying that alterations in integrin subunit mRNA are related to similar alterations in the expression of integrin subunit polypeptides. Attempts will be made to correlate differences in integrin subunit expression with the growth and invasive characteristics of these seven cell lines.

54. USE OF ALTERNATIVE TREATMENTS IN CFS

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Objective: To determine the extent of use and perceived effectiveness of alternative treatments in CFS compared to controls.

Methods: Subjects consisted of 104 patients with CFS (based on the CDC criteria) and 42 healthy controls. Detailed questionnaires were administered which included questions on demographics, activity level, stressful factors and 99 types of alternative therapies. The alternative or allopathic remedies consisted of non-prescription remedies and other non-medical healing techniques. The CFS patients had on average been ill for 4 years, were 40 years old and 70% were female.

Results: CFS patients and controls were well matched for age, gender, marital status, education and types of employment. The following treatments were used significantly more frequently in CFS compared to controls: yeast-free diet, anti-yeast medication, high dose multivitamins, minerals, lactobacillus and evening primrose oil. Subjects perceived that these therapies resulted in major improvement in only 12% of CFS but 36% of controls. They had little or no effect in 75% of CFS and 48% of control subjects. The CFS patients stated that alternative therapies were used because other approaches had not worked (40%) or because of desperation (30%). CFS patients revealed the use of alternative therapies to their physicians more frequently than did the controls (83% vs 35%, p=.002).

Conclusions: CFS patients commonly use alternative treatments because nothing else has been beneficial. These treatments are expensive and ineffective.

55. THE CLINICAL PRESENTATION OF PACEMAKER DEVICE FAILURE

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The optimal approach to the recall of a pacemaker or components of a pacemaker system is unknown. We observed a failure in 40(23%) of 168 implanted pulse generators (IPG) within a series of 'soft top' devices (Telectronics Inc.). In 70% of IPG, failure manifested as total loss of output. Failure presented in the emergency room (ER) in 11 IPG (7 requiring temporary pacing) and was found incidentally in 29 IPG (clinic). Pace dependency was defined as an escape heart rate < 40 bpm prior to failure, drug use refers to digoxin, ß-/calcium channel blocker or antiarrhythmic, NO refers to no output at presentation:

	ER (N=11)	Clinic (N=29)
Pace Dependency	30%	16% p=0.31
Drug Use	90%	50% p=0.03
NO	91%	50% p=0.02

There were no sudden deaths in the IPG failure presentation group. Among the 168 devices implanted, 26 patients died prior to device replacement with one sudden death in a patient with significant heart disease.

Conclusions: Documented pacing device failure is not associated with sudden death in patients with apparent pace dependency. Significant symptoms and emergency room presentation occurred in 40% of patients with failed devices. Pace dependency did not reach statistical significance in predicting clinical presentation at the time of device failure. Use of cardioactive medications predicted a poor response to the paroxysmal loss of device output.

56. PREOPERATIVE VASCULAR STUDIES TO DETERMINE THE LEVEL OF LOWER LIMB AMPUTATION AND FUNCTIONAL OUTCOME OF BELOW KNEE AMPUTEES

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Preservation of the knee joint is important in lower limb amputation. Vascular studies are used to determine the optimal level of amputation. An eight year retrospective study on 135 below knee amputees was carried out to evaluate 1) the preoperative Doppler studies and transcutaneous oximetry results as indicators of wound healing, 2) the functional outcome of the amputees. Patients' chart reviews and interviews with survivors were conducted. The ankle/ brachial index was found to be of limited value in the determination of the level of amputation. Transcutaneous oxygen pressure of >30mmHg was a good indicator of successful healing, whereas that of 20-30mm Hg warrant further consideration. With a minimum follow up of six months, the ambulatory status was found to be dependent on the aetiology of limb loss, the state of the other limb, the general health and the age of the patient.

57. PROGNOSTICATION OF SURVIVAL IN ADVANCED CANCER

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Estimating life expectancy for patients with terminal cancer is a difficult yet important task for medical personnel. The purpose of the study was to determine whether certain disease status indicators correlated with length of survival in a palliative care unit (PCU). The study was undertaken on the impetus that uncovering objective measures of disease burden would aid physicians in their accuracy in predicting of prognosis so that they could decide who should be considered for admission to a PCU. Moreover, a more accurate prediction of the terminal phase of cancer would allow for planning of appropriate care programs and providing options for terminally ill patients.

The study was conducted retrospectively using charts from patients who died in the PCU at the Grace Hospital in 1993 (n=147). Data collection was grouped into six subcategories. These subcategories included, 1)patient characteristics 2)relevant diagnostic dates 3)disease status (site of primary, type of tumour, site of metastases) 4)past treatment 5)signs and symptoms upon admission and 6)activities of daily living. The first stage of the analysis consisted of characterizing and constructing patient profiles for both extremes on the time scale of length of survival in the PCU (length of survival <7 and <15 days and >29 and >60 days). The second stage of the analysis is currently underway and involves regression analysis of the data.

Current analysis suggests that certain indicators are more typical of either a short or long length of survival in the PCU at the Grace Hospital. Liver involvement (liver metastases, jaundice, edema, ascites, hepatomegaly, and elevated liver function tests) occurred more frequently in those patients who fell into the shorter survival group. Similarly, lung involvement (lung metastases, dyspnea, and oxygen therapy) was also more frequently observed in this group. In addition, compromised nutritional status (poor appetite/anorexia, nausea, vomiting, and dysphagia) was commonly observed. By comparison, the most prominent features of those individuals with the longest length of survival in the PCU were either bony involvement (bone metastases and fractures) or neurological involvement (abnormal reflexes and power, diplopia, cranial nerve palsies, and paralysis).

The conclusion from this study is that terminal cancer patients with vital organ involvement such as liver or lung have a poorer prognosis than those patients with non-life threatening system involvement such as abnormalities of the neurological system or bony involvement.

58. STUDIES OF THE 3' PORTION OF FIBRONECTIN

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Smooth muscle cell (SMC) migration and intimal cushion formation seen in the ductus arteriosus (DA) is correlated with increased fibronectin synthesis. The increased fibronectin synthesis is not related to increased mRNA stability and is in fact related to decreased mRNA levels in DA relative to aortic (Ao) SMCs. Hence, the increased synthesis can be attributed to increased mRNA translation. Dr. Rabinovitch's lab has shown that a binding factor binds to an AU-rich sequence (UUAUUUAU) in the 3' UTR of fibronectin. In order to show that the AU-rich sequence affects translational efficiency, the U's in UUAUUUAU were changed to G's (using PCR mutagenesis) and this mutant sequence was introduced into the 74m-pBLCAT2 plasmid. DA and Ao SMCs are now being prepared to be transfected with this plasmid and CAT assays performed to determine if there are any differences in translational efficiency. More specifically, the hypothesis is that the AU-rich sequence acts as a repressor element. If it is mutated, then it is expected that translational efficiency will increase. Furthermore, if it is the only factor affecting translational efficiency, then DA and Ao SMCs transfected with the mutant will show similar reporter gene activity.

Studies were also done to determine the maximum transcription/translation efficiency in response to varying concentrations of Il1-beta (0 ng, 100 ng and 300 ng of Il1-beta) using the following construct:

//---TK Promoter---CAT Gene---3' Portion of Fibronectin---//

Preliminary results indicate that progressively higher concentrations of Il1-beta suppresses CAT activity.

59. EFFECTS OF GAMMA-HYDROXYBUTYRATE (GHB) IN HYPOVOLEMIA

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Administration of GHB following hemorrhage was previously shown to effectively restore Mean Arterial Pressure (MAP) and Cardiac Output (CO) without an increase in Total Peripheral Resistance (TPR). The present study was undertaken to test the hypothesis that GHB directly improves cardiac contractility following hemorrhage.

Methods : Femoral artery, jugular vein and carotid artery were cannulated in 28 male Wistar rats. A carotid cannula was advanced into the left ventricle and connected to the *Digi-Med*™ Heart Performance Analyser (Micro-Med Inc., USA). After removal of 35% of the estimated blood volume, animals received infusion of 0.9% Saline (N=9), GHB solution (400 mg/kg) (N=10), or 7.5% NaCl/10% Dextran 70 solution (N=9). Their recovery was followed for the next 2 hr. MAP and central venous pressure (CVP) were monitored throughout the experiment. The following derivatives from the left ventricular pressure trace were obtained: Ventricular End Diastolic Pressure (VEDP), Ventricular Peak Systolic Pressure (VPSP), Heart Rate (HR), Maximum dP/dT (dP/dTmax), Ventricular Pressure at dP/dTmax (P@dP/dTmax), and Maximum ventricular dP/dT/P (MAXdP/dT/P).

Results : As in our previous studies, infusion of GHB caused a stable elevation in MAP. The pressor effect was greater than that provided by the infusion of normal saline. Administration of hypertonic solution was also effective in restoring MAP, but this effect was transient and disappeared by 45 min post-infusion.

GHB-treated rats had a 6% higher HR than controls. However, it is unlikely that changes in HR were solely responsible for the 35-40% increase in MAP. Treatment with GHB led to an increase in VPSP to 102±3.5% of the initial level, while treatment with hypertonic or normal saline did not result in any stable improvements. The GHB-treated animals also exhibited an increase in dP/dTmax, despite an increase in ventricular afterload. Neither CVP nor VEDP in both GHB and hypertonic saline-treated groups were significantly different from the normal saline-treated animals, except for a short period of time immediately after the infusion. This corresponded to a transient decrease in MAXdP/dT/P and was probably due to a transitory fluid shift into the vascular compartment, and thus, increase in venous return. P@dP/dTmax was significantly increased by infusion of either GHB or hypertonic solution. This suggests if anything, that the increase in P@dP/dTmax was mainly due to an increase in VPSP, since no consistent increase in VEDP was observed. This, in turn, may indicate an increase in TPR, which contradicts our previous experimental findings.

Overall, an increase in dP/dTmax with the simultaneous increase in MAP, in the absence of an increase in VEDP, seems to indicate that GHB increases myocardial contractility. However, changes in MAXdP/dT/P and P@dP/dTmax did not provide a definite support to the above hypothesis. On the other hand, the fact that GHB group also exhibited an elevation in HR shows that GHB effects are probably multifactorial. In conclusion, these experiments further confirm that GHB has a unique ability to elevate blood pressure in hemorrhagic shock. However determination of the actual mechanism of action requires additional efforts.

60. RECOVERY OF OVARIAN FUNCTION FOLLOWING AUTOLOGOUS BONE MARROW TRANSPLANTATION

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Bone marrow transplantation (BMT) is a potentially curative therapy for selected types of leukemia and lymphoma. Progress has resulted in the long-term disease-free survival or cure of an increasing number of patients therefore, more attention must be paid to the long-term effects of this therapy such as the loss of ovarian function. This common complication of BMT is thought to be due to the high doses of cytotoxic agents and total body irradiation (TBI) used as conditioning before BMT. While many women experience premature ovarian failure following BMT, little information is available on the ultimate effect of treatment on the ovarian function of recipients.

Twenty-four women who had received an autologous BMT for hematological malignancy at the Toronto Hospital between 1987 and 1992 were studied. Data was analyzed with respect to age, the type of pre-BMT conditioning therapy, and resumption of ovarian function as determined by return of menses, absence of menopausal symptoms, pre-menopausal hormone levels and pregnancy.

Nine patients were transplanted for acute myelogenous leukemia, 9 for Hodgkin's disease and 6 for non-hodgkin's lymphoma. Conditioning regimens consisted of VP-16 (60mg/kg); melphalan (140-180mg/m^2); and 0 (n=12), 300 cGY (n=1), 500cGY (n=9) or 1200cGY (n=2) TBI. Two women of the AML group (22.2%) regained ovarian function with an average age at transplantation of 26.9 years, recovery at an average of 51.5 months post-BMT and one pregnancy occurring at 62 months post-BMT. Of the 9 Hodgkin's patients, 5 (55.6%) regained ovarian function with an average age at transplantation of 28.2 years, recovery at an average of 13 months post-BMT and one pregnancy occurring at 29 months post-BMT. None of the NHL patients, transplanted at an average of 33.3 years, regained ovarian function.

In all, 7 women (29.2%) recovered ovarian function. Patients receiving TBI (n=12) had lower recovering of ovarian (16.7%) as compared to patients not receiving TBI (n=12) (41.7%) suggesting that TBI has greater ovarian toxicity than chemotherapy. Recovery tended to occur in women transplanted at a younger age (<29 years, ave. 22.4 years) and tended to occur early (ave. 24 months post-BMT) While the greatest rate of recovery was in the first year following transplantation, recovery was shown to continue at a steady rate up until 5 years post-BMT. Given that many of the women who did not recover ovarian function had not been given a recent trail off HRT, a number of these women may have experienced return of ovarian function if given an additional trial off HRT. Recovery of ovarian function following BMT is possible and may occur more commonly than was previously thought.

61. THE SIGNIFICANCE OF FETAL CHOROID PLEXUS CYSTS: IS AMNIOCENTESIS INDICATED IN ALL CASES?

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Fetal choroid plexus (CP) cysts are not an uncommon incidental finding in routine mid-trimester obstetric ultrasounds. CP cysts have been associated with trisomy 18, and other devastating chromosomal abnormalities, but usually other gross anatomic abnormalities are also present on the sonogram. The significance of isolated CP cysts (i.e. with no other sonographically detectable abnormalities) is far less certain. The purpose of this study was to determine whether fetuses with isolated CP cysts are at an increased risk for congenital abnormalities, and therefore, warrant amniocentesis (a procedure which carries a 1 in 200 risk of miscarriage).

Over a 13 month period (April 1993 to April 1994), all pregnancies referred for routine second trimester ultrasounds at Mount Sinai Hospital were assessed for the presence of fetal CP cysts. Clinical follow-up during and at the conclusion of the pregnancies was conducted to determine whether fetuses with CP cysts had normal genotype and phenotype.

There were 45 fetuses with CP cysts, giving an approximate incidence of 2%. Fifty-one percent of these had follow-up fetal ultrasounds. In 74% of these follow-up scans, the CP cysts had resolved. There were no chromosomal abnormalities and only 2 neonates had phenotypic abnormalities noted at birth. One abnormality was a facial haemangioma in the distribution of the trigeminal nerve. This fetus had normal genotype on amniocentesis and had a persistent CP cyst. The other fetus, born with left hydronephrosis had normal Triple Screen Test results and CP cysts which resolved during pregnancy. One pregnancy showed intrauterine growth retardation and 3 neonates were born with low birth weight.

From our study, isolated CP cysts do not appear to confer increased risk for chromosomal abnormalities. Other authors have recommended amniocentesis for all fetuses with CP cysts. Our data do not support this recommendation, and we are conducting an ongoing prospective study to further investigate this important clinical controversy.

62. VEROTOXIN: A POSSIBLE THERAPEUTIC PROTOCOL FOR OVARIAN CANCER

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Cancer of the ovary is the fifth leading cause of cancer death in women, and the most prevalent gynecological cancer. Since the introduction of the platinum chemotherapy agents twenty years ago, there has been little progress in its treatment and this is reflected in the fact that the survival rate in 1991 was only slightly better than in the past two decades. Today only approximately fifty percent of women with stage III/IV ovarian cancer respond to chemotherapy, and most of those who do have a recurrence of the disease within 12-18 months, at which point the problem of drug resistance presents itself. These statistics indicate the need for alternate treatment plans. Since large scale screening for ovarian cancer is not financially feasible due to the relatively low occurrence of ovarian cancer versus other cancers the need for improved treatment becomes more vital. One possible alternate treatment involves the use of verotoxins. Verotoxins, exotoxins produced by non invasive strains of *E. coli,* have been shown to have anti-neoplastic activity against certain cell lines. The question remained whether this anti-neoplastic activity extended to ovarian cancer cells. The most potent verotoxin, verotoxin 1, binds to a glyco-lipid receptor, globotriaosylceramide (Gb_3). The purpose of this study was to analyze the Gb_3 receptor of ovarian tissues, both neoplastic (surface epithelial-stromal tumours) and non-neoplastic. Ovarian samples of the following types were analyzed for Gb_3 receptor content: normal, serous cystadenomas, serous cystadenocarcinomas, mucinous cystadenomas, mucinous cystadenocarcinomas, endometrioid cystadenomas, and endometrioid cystadenocarcinomas. Gb_3 was extracted from the ovarian tissues samples, and the Gb_3 levels in the different samples were determined using a verotoxin overlay.

Interestingly while Gb_3 was present in some of the normal ovarian tissue samples, the amount of Gb_3 in the cystadenomas and cystadenocarcinomas specimens was greater. In addition there was marked variability of Gb_3 receptor levels amongst the different types of neoplasms.

This research showed that neoplastic ovarian cells have increased levels of Gb_3 receptors compared to non-neoplastic cells, indicating that ovarian cancer cells may more susceptible to verotoxin than their normal counterparts. In addition, there was marked variability of Gb_3 receptor content between different tumour types suggesting differing susceptibility between neoplasm types.

63. EFFECTS OF VITAMIN E SUPPLEMENTATION IN HAMSTERS WITH THE DILATED CARDIOMYOPATHY DEFECT

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Ventricular dilated cardiomyopathy in the golden Syrian hamster is a common animal model for heart failure. Oxidative stress and inadequate antioxidant protection has been implicated in the etiology of the golden Syrian hamster model of the dilated cardiomyopathy defect.

The purpose of this experiment is to determine if treatment with Vitamin E could elevate the decreased levels of Glutathione Peroxidase in hamsters expressing the dilated cardiomyopathy defect and/or elevate levels of Glutathione Peroxidase in control hamsters without the defect. Research last summer demonstrated that the DCM defect imposes an oxidative stress on hamster hearts leading to decreased GPx production. Vitamin E has been shown to stabilize the mRNA of GPx, and in the presence of an oxidative stress, should maintain GPx levels at near-normal values.

26 Syrian hamsters were studied, of which 13 had the dilated cardiomyopathy defect and 13 did not have the cardiomyopathy. Seven of the hamsters in each group received daily injections of 70mg/kg Vitamin E for four weeks. The other hamsters received no supplemental Vitamin E. Following treatment, the hamsters were sacrificed, and the concentration of GPx in the hearts was measured.

The difference in GPx levels per unit protein between dilated cardiomyopathic hamsters receiving Vitamin E (47.223U/mg protein) and dilated cardiomyopathic hamsters receiving only ethanol (33.329 U/mg protein) was statistically significant (P=9.79E-3). The difference in GPx levels between dilated cardiomyopathic hamsters receiving only ethanol (33.329) and control hamsters receiving only ethanol (56.332) was statistically significant (P=2.431E-4). The hamsters with the dilated cardiomyopathy defect which received daily injections of Vitamin E had their GPx levels statistically elevated to a level that was not significantly different from control hamsters.

Injection of control hamsters with Vitamin E had no significant effect on the GPx levels. The control hamsters do not have the excess oxidative stress that the hamsters with the dilated cardiomyopathy defect have. The control hamsters therefore meet their daily Vitamin E requirements through their regular diet, whereas the dilated cardiomyopathic hamsters are unable to meet their Vitamin E requirements. The excess oxidative stress of the dilated cardiomyopathy may push Vitamin E requirements past the amount contained in a normal daily diet. These results suggest a potential role for Vitamin E supplementation for heart failure.

64. PORTAL ENDOTOXEMIA STIMULATES THE RELEASE OF A NOVEL LIVER DERIVED FACTOR THAT INDUCES MACROPHAGE-MEDIATED IMMUNOSUPPRESSION

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Infection, arising in association with an acquired state of transient but profound immune dysfunction, is a common and lethal complication of critical illness. The pathogenesis of these immunologic alterations is poorly understood. Both impaired mitogen-induced lymphocyte proliferation and altered synthesis and release of pro-inflammatory cytokines are common findings.

We have previously shown that infusion of gram-negative organisms into the portal, but not systemic circulation of the rat produces impaired mitogen-induced lymphocyte blastogenesis by a macrophage (Mø) dependent mechanism. This observation suggests that the liver releases a circulating factor that can induce immunosuppressive activity in Mø's. The present studies were undertaken to establish this hypothesis.

Anesthetized rats received 3 X 10^8 killed *Pseudomonas aeruginosa* via the portal vein (PV) or inferior vena cava (IVC). Non-operated animals served as controls. Plasma collected 2 hours later was added to naive alveolar Mø's cultured in supplemented RPMI. At 24 hours, plasma was removed, fresh medium added and the Mø's incubated a further 24 hours. Supernatants were then added to Con A-stimulated splenic lymphocytes to evaluate suppressive activity as measured by uptake of [^{3}H] Thymidine. TNF release by naive alveolar Mø's activated with 10 µg/µL endotoxin was measured by ELISA. Results are shown (mean ± SD).

TREATMENT GROUP	[^{3}H] THYMIDINE UPTAKE Counts per Minute X 10^3 (n=4)	TNF RELEASE ng/mL (n=2)
Control	47.7± 11.6	3.9 ± 1.6
PV Injection	0.1 ± 4.5 *	2.6 ± 1.2
IVC Injection	48.9 ± 17.1	4.5 ± 1.9

*$p<0.05$

These studies demonstrate that the liver can release an as yet uncharacterized factor (termed Hepatic Suppressor Inducer Factor) that reproduces several of the immunologic abnormalities of critical illness and implicates the liver as a key organ of immune homeostasis following overwhelming infection.

65. RISK FACTORS LEADING TO RAPIDLY PROGRESSIVE CORONARY DISEASE IN CHINA: COMPARISONS WITH CANADIAN POPULATION

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The focus of cardiology practice in China has switched from valvular and congenital diseases to coronary artery disease. The recent exponential increase in coronary artery disease may in part be due to the changes in lifestyle in China, where it is presently undergoing a rapid phase of economic reform and Westernization. Percutaneous Transluminal Coronary Angioplasty (PTCA) is a surgical procedure to reopen coronary vessels that are partially occluded by severe atherosclerotic plaques. Therefore, patients undergoing PTCA represent individuals who have severe atherosclerosis. A study of these patients allows for examinations of i) the risk factor profile, ii) the major factors leading to changes in disease profile and iii) the angiographic consequences of the disease process.

In the present study, a standard questionnaire targeting "angioplasty" patients with lesions in the proximal one-third of the left anterior descending coronary artery was designed. The questionnaire included information on risk factors, operation details, pre-op/post-op conditions and treatment, and restenosis rate. The data collected may reveal whether modifiable risk factors, such as hypercholesterolemia and smoking, are associated with the recent increase in coronary artery disease. The data collected was also compared to similar data from patients in Canada enroled in the Canadian Coronary Atherectomy Trials (CCAT).

Thirty-four percent of the patients of the study group had two or more risk factors. The major risk factors in the group were smoking, hypertension, and hypercholesterolemia. However, family history and diabetes were not significant risk factors (<10%). Therefore, this study may point to a link between the changes in lifestyle (smoking and diet) and the increase in coronary disease patients.

66. WHOLE ABDOMINOPELVIC RADIOTHERAPY IN LATE STAGE EPITHELIAL OVARIAN CANCER PATIENTS PATHOLOGICALLY NEGATIVE AT SECOND LOOK LAPAROSCOPY

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Current primary therapy for patients diagnosed with stage 3 and 4 epithelial carcinoma includes maximal cytoreductive surgery and adjuvant platinum based chemotherapy. Reported cure rates remain disappointingly low at about 20%. At present, there is no second line therapy proven to improve cure rates among these patients. The potential of WAR to to offer curative benefit in patients who have had a favourable response to first line treatment has been suggested. This retrospective clinical series examines the role of consolidative WAR in patients who had minimal or no disease at second look surgery.

The records of 23 patients with stage 3 ovarian cancer who underwent second look laparoscopy at Sunnybrook Health Centre were reviewed. All patients had undergone debulking surgery and platinum chemotherapy prior to second look. Fifteen patients went on to receive second line WAR and 8 did not receive further therapy. Of the 15 patients(cohort A) who did receive WAR, 14 had no pathological disease at second look laparoscopy and one had positive peritoneal washings only. Of the 8 patients(cohort B) not receiving WAR, 4 had microscopic disease and 2 had dense adhesions at second look surgery, 1 refused WAR and 1 experienced extreme toxicity on her first fraction of radiotherapy. Differences in proportion among the 2 cohorts was not significant for certain possible risk factors including age, histology, grade and stage. In cohort A, 10 patients were optimally debulked at primary surgery(<=1cm) and 5 patients were suboptimally debulked(>1cm). In cohort B, 3 patients were optimally debulked and 5 patients were suboptimally debulked.

As of August 1994, median follow-up time from initial surgery for all patients was 21.3 months(range 8.7-39.9). Median times to recurrence for cohort A and B were 18.3mths and 14.6mths respectively. The incidence of clinical recurrence in cohort A was surprisingly greater than cohort B. Eight of 15 patients recurred in cohort A, all within the irradiated field. Three out of 8 patients relapsed in cohort B. For cohort A, progression free survival at 33 months was 45.3% and overall survival was 62.3%. Progression free survival for cohort B at 33 months was 50%.

Toxicity due to WAR was acceptable. Four patients experienced severe acute toxicity. Two patients failed to complete the planned treatment. One patient required laparotomy for small bowel obstruction due to radiation enteritis.

Conclusion: Reported relapse rates and progression free survival in this series among patients pathologically negative at second look surgery and treated with WAR are not different from those reported in patients pathologically negative at second look and receiving no further therapy. Whole abdominal radiation is not effective in patients with complete pathological response to chemotherapy.

67. RESCUE OF OLIGODENDROCYTES FROM APOPTOTIC CELL DEATH BY (-)-DEPRENYL

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The term "apoptosis" was introduced in 1972 in order to distinguish between cells which died in a organized fashion as a part of the normal development of tissue, from those cells which died through necrosis in response to pathological insult. A question which has arisen over the last decade is whether any of the cell death that occurs in the mammalian nervous system in neurodegenerative disease is due to apoptosis rather than necrosis. Recent studies have shown that the Parkinsonian drug (-)-deprenyl can mediate neuronal rescue by a process independent of MAO-B inhibition through interference of the process of apoptosis. This finding suggests that (-)-deprenyl may similarly rescue other cell types of the CNS from apoptosis, namely oligodendrocytes. Recently, Barres et al. have found that 50% of newly formed oligodendrocytes die in the developing rat optic nerve between P4 and P12 by the process of programmed cell death. The ability of (-)-deprenyl to rescue oligodendrocytes from cell death was investigated in this in vivo model of rat optic nerve as well as in an in vitro model of cultured rat cortical oligodendrocytes. Preliminary results have shown that 1 X 10 -9 M (-)-deprenyl increased the survival of cultured oligodendrocytes by 60-70% over control cells following insulin withdrawal. In addition, rats receiving daily intraperitoneal injections of 0.01 mg/kg (-)-deprenyl appeared to show an increase of 25-30% in total glial cell numbers in sections of optic nerve viewed by LM.

68. COUPLING POTENTIALS IN CA1 NEURONS DURING CALCIUM-FREE INDUCED FIELD BURST ACTIVITY

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Before evidence for chemical synaptic transmission within the central nervous system (CNS) had been obtained, neuronal communication was thought to be mediated solely through direct electrical interactions. Although it now appears that in the CNS a large part of cellular communication is through chemical synapses (especially long range information transfer), the anatomical arrangement of neurons in many regions of the brain and the presence of proteins (gap junctions) that can electrically and metabolically connect cells within the CNS, suggests that direct electrical interactions may be involved in local modulation of cellular activity.

To study the role of direct electrical interactions between neurons, we employed an *in vitro* model of epilepsy characterized by spontaneous seizure-like events, in the absence of chemical synaptic transmission. Whole cell recordings from hippocampal CA1 neurons in calcium-free medium revealed the presence of small depolarizations (0.5-5 mV, termed **spikelets**), that were invariant with membrane voltage. Spikelet presence was positively correlated with dye coupling between pyramidal cells. The sequence of spikelets were in all instances highly structured, and normally between two and four spikelet amplitudes were recorded from each neuron. This pattern of spikelet discharge was indistinguishable from action potential firing, suggesting a neuronal basis for their generation. Consideration of averaged spikelet waveforms suggests that they could arise from differentiated action potentials. We have been able to estimate the contribution of resistive and capacitive components of this direct electrical interaction. These findings suggest that a potential mechanism of direct electrical interactions may exist in the mammalian CNS, which under certain conditions could promote seizure-like activity through synchronization of neuronal firing.

69. AN ANALYSIS OF GONADAL AND SEXUAL FUNCTION IN MALE, ALLOGENIC BONE MARROW TRANSPLANTATION RECIPIENTS

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Bone marrow transplantation (BMT) is becoming an increasingly viable treatment option, and offers a possible cure, for patients with a number of malignant and non-malignant haematological disorders. Since there are an increasing number of long term survivors of BMT, there is a need to redirect emphasis from survival to quality of life issues of survivors. Sexuality issues are one of the key areas affecting quality of life in the general population. Reproductive capabilities and sexual functioning may be affected adversely in this population by the original disease, the pre-BMT regimen which includes chemotherapy and total body irradiation, or post BMT complications. The purpose of this study was to evaluate the status of sexual function of male patients following BMT, ascertain the extent of the problem and see if any correlations exists between the degree of sexual function and a variety of other parameters. The final purpose was to discover if gonadal and sexual functioning recovers, and the time frame for the recovery.An extensive questionnaire was designed and mailed to male patients, more than six months post BMT, who were over 18 years old. The survey included questions about demographic data, pre-BMT regimens, and post BMT outcomes. The survey included a medical sexual history, and psychosocial issues . Given the personal and sensitive nature of the questions, the survey could be completed anonymously. Preliminary results, of this ongoing study, indicate that of the 92 who were mailed the survey, 56 returned the surveys. Since more than 90% of the patients identified themselves, the opportunity exists to continue further investigations and obtain information from medical charts. 40% of those returning the questionnaire indicated a decrease in sexual function, and 20% of this group indicated that sexual function had never returned.. However, the other 80% indicating reduced functioning following the BMT, indicated that sexual function returned usually within 6 months after the BMT. Thus, sexual dysfunction occurs in a significant number of the male patients following BMT the issue needs be discussed before their transplants. Encouragingly, many find that their level of sexual function returns within the year after their BMT. This study indicates that individuals who had a BMT within the last 6 months who were initially excluded from the study, should be followed since they are the ones currently experiencing the most difficulties.

70. DIETARY FACTORS AND PROSTATE CANCER IN JAPAN VERSUS CANADA

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Introduction: In Japan and other Asian countries prostate cancer is rare. However, in Western counties, such as Canada, prostate cancer is a major killer. The cancer etiology is not completely understood but hormonal factors play an important role. Recently, several dietary factors have been shown to alter hormone production, metabolism and function at the cellular level: macronutrients such as dietary fat, and micronutrients, such as diphenolic plant estrogens (lignans and isoflavones). The presence of these dietary factors varies tremendously between Japan and Canada. Thus, we studied the potential connection between prostate cancer (using PSA levels as a marker of risk) and the presence of specific dietary macro- and micronutrients.

Purpose: To study the connection between diet and prostate cancer.

Methods: Fifty Japanese men between the ages of 30-95 were recruited from urban and rural areas of Okinawa, Japan, which has an extremely low incidence of prostate cancer. Subjects were healthy and not on any medications. Most subjects completed a 3 day diet history (food record) of their regular diet. Height, body weight, blood pressure and PSA levels were recorded. They were compared with Canadians taking part in mutual studies.

Results: Japanese subjects consumed much lower levels of fat and much higher levels of carbohydrate than Canadian subjects. The main foods responsible for the dietary differences were rice and soy products consumed by the Japanese. Soy consumption was over 30 g/day in the Japanese whereas this amounted to less than 1 g/day in the Canadians. Blood work revealed increased PSA levels in the Canadian subjects versus the Japanese.

Conclusion: The Japanese diet contains several factors that may reduce the risk of prostate cancer. Dietary fat may be one of these compounds. However, the plant lignan and isoflavones, which are present in large quantities in soy products, and have weak estrogenic and antioxidative effects, may play a prominent role as anti-neoplastic agents in the Japanese diet.

71. AN EVALUATION OF THE ASSOCIATION BETWEEN CYTOMEGALOVIRUS (CMV) MEDIATED MARROW FAILURE AND PARTICULAR CMV STRAINS

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Identifying patients pre transplant who are carrying a particularly virulent form of cytomegalovirus (CMV) would provide indications for aggressive antiviral therapy, which because of its cost and side effects should not be used prophylactically on all patients. To do this, however, first requires the identification of what constitutes virulent forms of the virus. Previous studies suggest that the variable clinical outcomes manifested by immune compromised individuals infected with CMV is related to difference in CMV strains encoded by envelope glycoprotein gB genes. This study seeks to retrospectively identify marrow transplant patients infected with CMV who developed marrow failure and determine whether a particular CMV gB type is associated with this outcome compared to infected patients who did not develop marrow failure.

Patients with documented viremia who did not receive any antiviral prophylaxis were included. CMV isolates stored on these patients were retrieved and the gB sequence was amplified and isolated by PCR. The amplified sequence was subjected to a restriction enzyme digest, yielding banding patterns on acrylamide gels which distinguished gB types 1-4.

One hundred and forty-four patients were allotted into the study. The results indicated that 57.7% of patients who manifested lung disease were infected with CMV of gB type 1, whereas in patients with pure viremia, only 35.5% were of type 1.

These results suggest that gB type 1 has a greater tendency than other types to infect the lung. From this study then, it would appear that gB envelope glycoprotein variation is an influential factor in determining viral tropism.

72. ACUTE MOOD IMPROVEMENT AFTER AMPHETAMINE AND METHYLPHENIDATE IN NARCOLEPSY

J.Zwicker, D. Bruck, J.D. Parkes and R.J.Broughton, Sleep Clinic at the Maudsley Hospital, Human Neurosciences Research Unit of the University of Ottawa

Although stimulants are the primary treatment for narcolepsy, no studies have formally evaluated mood changes that may occur in these patients after ingesting either dextroamphetamine(D-AMP) or methylphenidate(MPH). This study sought to evaluate the mood altering effects of therapeutic doses of D-AMP and MPH in narcoleptics and to establish whether or not the effects of the drugs differ.

A questionnaire package was mailed to narcolepsy patients who had attended the Maudsley Hospital in London, England in the previous ten years or the sleep clinic at the Ottawa General Hospital. The package contained two Profile of Mood States (POMS) questionnaires which evaluated six mood factors and eight additional questions rating a variety of feelings. Subjects were instructed to complete side A of the questionnaire after breakfast and just before taking their normal morning dose of stimulant medication. Side B was to be completed 90 minutes following stimulant medication intake. In total, 20 patients on D-AMP and 20 patients on MPH returned the questionnaires completed properly.

The raw scores on the six mood factors and the eight adjectives obtained both before and after the administration of medication were analysed using independent or paired t-tests as appropriate.

No significant differences were found between the effects of the two stimulants. When the data from D-AMP and MPH were combined, significantly higher ratings on the POMS factor of Vigor-Activity and the adjectives of confident, talkative and competitive were found. Lower ratings after medication were noted for the POMS factors of Fatigue-Inertia, Depression-Dejection and Confusion-Bewilderment (all p levels < 0.001).

It may be concluded that, in narcoleptics, both D-AMP and MPH have significant and similar impacts on subjective assessments of three broad aspects of mood: positive affect, activity level and clarity of thought. These effects are similar to those previously reported in normal subjects as well as in certain patient populations. The findings suggest a possible therapeutic role of stimulant medication not only for the treatment of excessive sleepiness but also for the depression and cognitive deficits that may be associated with narcolepsy.

73. THE GROWTH OF AN EPIPHYSEAL PLATE ALLOGRAFT

Illustrator: Paulette Dennis
Supervisors: Dr. Vaughan Bowen, Toronto Western Hospital, (Medical), Dr. Linda Wilson-Pauwels, (Medical Art)

Deformity resulting from congenital anomaly, disease or injury to the epiphyseal plate is one of the most difficult problems in orthopaedic surgery. The possibility of epiphyseal plate transfers has interested orthopaedic surgeons for years, but it is only since the development of microvascular surgery techniques that predictable post-op viability can be achieved.

Variables that govern the amount of growth achieved after successful transfer are age, sex, inborn growth potential,anatomical location, etc. of an epiphyseal plate. In the clinical situation, it would probably never be possible to match exactly the growth potential of the donor epiphyseal plate to that of the recipient site. For this reason, a series of experiments have been conducted to investigate the effect of known variables on growth after microvascular epiphyseal plate transfer.

It is hypothesized that the rate and duration of growth in an epiphyseal plate transfer will be a function of the donor epiphyseal plate irrespective of the recipient site location to which it is transferred.

To illustrate this hypothesis, I have visually compared two similar chondrocytes in the proliferative stage of bone growth. The host chondrocyte has three receptors for growth factors, and the donor has only one receptor, implying that the donor tissue will be less affected by a homogeneous environment of growth factors than the host. I have interpreted the hypothesis through the use of dynamic movement of line, changes in scale, colour, and symbols.

74. LIVER REGENERATION

Illustrator: Beverly Nash
Supervisor: Dr. Claire Holloway, Women's College Hospital

Research into liver regeneration has been an area of interest for many years. The liver and its important role in detoxifying blood makes it vulnerable to damage. Whether this damage results from a viral origin (hepatitis) or a chemical origin (alcohol), it is of great interest and use to understand how the liver regenerates.

Studies most recently have concentrated on regeneration of parenchymal cells or hepatocytes. It has been well documented how they divide in response to growth factors present in the liver. However, non-parenchymal cells are a relatively new horizon in liver regeneration research and it is these cells on which our research concentrates. If we are to understand the full picture of regeneration the contributions of these non-parenchymal cells and regeneration pattern must be studied. There are a variety of growth factors each with distinct actions, positive and negative, as well as synergistic and antagonistic. As such, the topic is complex which presents a challenge to produce clear and didactic illustrations.

My approach to depicting this research will be one detailed airbrush illustration with three acetate overlays. The overlays will depict the relevant growth factors, their relative concentrations and actions, as well as accompanying text where applicable. This illustration was produced under the direction of Dr. Linda Wilson-Pauwels and Dr. Claire Holloway.

75. CALCIUM RECEPTOR MICRODOMAINS MODIFIED BY MOBILE CHELATORS

Illustrator: Judy Sherwood
Supervisor: Dr. M.C. Wallace, Division of Neurosurgery

The illustration describes an hypothesis explaining how nerve cells succumb to oxygen deprivation caused by temporary obstruction of blood flow. Experimental findings support an hypothesis explaining 1) a mechanism by which calcium influx during hypoxia causes immediate cell death and 2) how a calcium chelator, BAPTA when given to tissue prior to an hypoxic episode, can block this process.

In hypoxia, there is an excessive release of the neurotransmitter glutamate which binds to receptor gated calcium channels on nerve cell membranes. These channels remain open allowing a prolonged influx of calcium. The calcium distribution within the cell assumes a gradient configuration, concentrations being the highest inside the channel pore. There is a calcium receptor-trigger situated near the inside of the pore of the NMDA receptor-calcium channel which has a low affinity for calcium. Under normal conditions calcium concentrations in the cell are too low to bind to this receptor and activate the trigger, but under such conditions as hypoxia, the calcium level in its vicinity is high enough to do so. This calcium receptor-trigger when activated initiates a cascade of cell processes which kill the cell.

When nervous tissue is pretreated with a calcium chelator BAPTA, and then subjected to an hypoxic episode, BAPTA binds calcium and removes it from the pore zone preventing activation of the trigger and the subsequent neurotoxic events.

76. BRACHIAL PLEXUS INJURIES IN THE NEWBORN

Illustrator/Author: C. Yee, B.Sc.
Supervisors: A.M. Agur, B.Sc.(OT), M.Sc., H.M. Clarke, M.D., Ph.D., F.R.C.S.(C), C. Curtis, B.Sc.(PT), L. Wilson-Pauwels, Ed.D.

My visual research project centers around the design of an illustration entitled "Brachial Plexus Injuries in the Newborn". The illustration will be used as a patient-parent educational poster at the Brachial Plexus Clinic at the Hospital for Sick Children, the only clinic of its kind in Canada. Between 1988 and 1992, 110 consecutive infants were assessed at the Brachial Plexus Clinic. The majority of these infants spontaneously recover sufficient arm function so as not to require primary plexus surgery. However, they do need special care and it is advisable that parents understand the anatomy of the brachial plexus and the type and consequences of the plexus injury.

The illustration "Brachial Plexus Injuries of the Newborn" is meant to be used as a teaching tool not only for parents but also for medical students to review their basic brachial plexus anatomy and some histology of the neuromuscular junction. The poster is composed of three elements: the anatomy of the brachial plexus from spinal cord to neuromuscular junction, the typical arm position of an infant with an upper brachial plexus palsy (Erb's palsy), and the different types of injuries sustained during a brachial plexus obstetrical injury. In an attempt to produce a didactic, dynamic, and aesthetically appealing illustration, several visual cues have been used: design, size and shape of objects, light and shadow, colour, and labeling. Without these visual cues, the artwork would be difficult and confusing for the viewer. Proper incorporation of these visual cues into an illustration serves to add clarity and emphasis to important parts of the illustration, thus enhancing the didactic qualities of the illustration.

NOTES

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